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Effectiveness of Feed Additive Usage of Antibacterial Agents in Swine and Poultry Production

By

Virgil W. Hays

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Foreword

It was as true - - - as turnips is.
It was as true - - - as taxes is.
And nothing's truer than them.

Charles Dickens

Documentation of the benefits of feed additive antibiotics for swine and poultry production is clearly needed by producers and feed manufacturers. Perhaps more importantly, documentation of the benefits is needed, if feed additive antibiotic usage is to be sustained against the seemingly constant regulatory pressures to ban their use. The enclosed report presents a 30-year summary of "Effectiveness" of feed additive antibiotics in poultry and swine production. It is a "Commissioned Paper" prepared by Dr. Virgil W. Hays, University of Kentucky for the Office of Technology Assessment, Congress of the United States. The poultry and swine industry is truly indebted to Dr. Hays for accumulating, digesting, and organizing the mass of data contained in his report. The use of feed additive antibiotics clearly continue to be beneficial in poultry and swine production.

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About the Author

The author received his early training in Animal Sciences at Oklahoma State University and the Ph.D. in Animal Nutrition at Iowa State University. He has held research and teaching appointments at Iowa State University and University of Kentucky and presently is Professor of Animal Nutrition and Chairman of the Department of Animal Sciences at the University of Kentucky.

Professor Hays has extensively studied the effects of antibacterial agents on performance of animals, development and transfer of antibiotic resistance and tissue clearance of antibacterial agents. He has written extensively on the biological effectiveness of antibacterial agents and factors affecting their responses.

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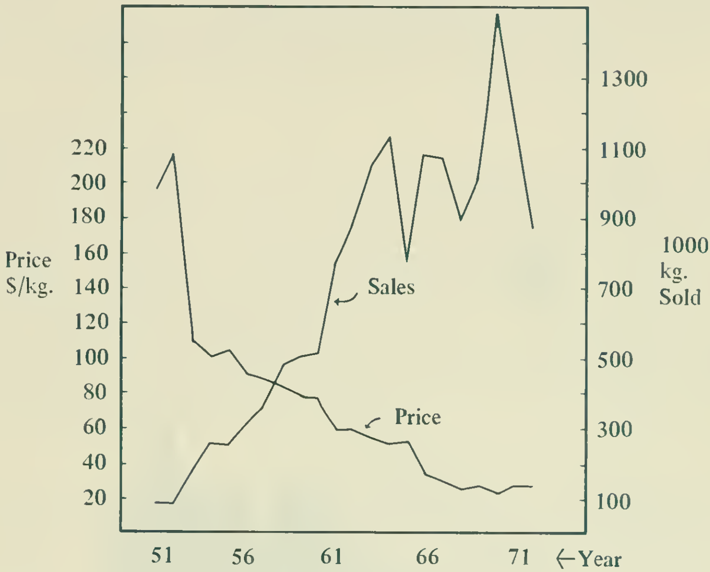
I. Introduction

Antibiotic feed supplements have been extensively used in every major livestock and poultry producing country for more than 27 years. In the United States alone, the nonmedical sales of antibiotics averaged 1.05 million kg annually between 1963 and 1972 (see figure 1).



U.S. Tariff Comm. 1951 - 1972

Figure 1. Average price and total sales of antibiotics for nonmedical uses, 1951 to 1972 (536).

In addition, substantial quantities of arsenicals and nitrofuran drugs are used. The wide acceptance of antimicrobial agents is attributable to the known benefits of increased growth rate, improved feed conversion and reduced mortality and morbidity due to clinical or subclinical infections.

Antibacterial agents commonly used in swine and poultry production as dietary additives include bacitracins, chlortetracycline, erythromycin, neomycin, oxytetracycline, oleandomycin, penicillin, streptomycin, tylosin, arsenicals and nitrofurans. Recently bambermycins and virginiamycin have been added to the approved list. Among those presently used, some are more effective as growth promoters than others. Other antibiotics have shown promise experimentally as effective additives; several which are not approved as feed additives are used as therapeutic agents.

The total number of antibiotics approved for use in livestock and poultry production, either as feed additives or for therapeutic usage, total about 14. This is a substantial number; however, Raper (428) reported that some 300 antibiotics had been described and partially evaluated by 1952; since then many others have been discovered and evaluated. Therefore, only a small percentage of antibiotics available has been found to have major application; the majority are unsuitable for one or more reasons, including low activity, toxicity to the host animal, resultant tissue residues,etc. Some may be quite effective but offer no particular biological advantage over those presently used; thus their development on an industrial level cannot be justified. Though the quantity produced and sold varies from year to year, about 40% of the antibiotics sold in the U.S. is for nonmedical uses, mainly as feed additives (see figure 2).

TOTAL AND NON-MEDICAL SALES OF ANTIBIOTICS

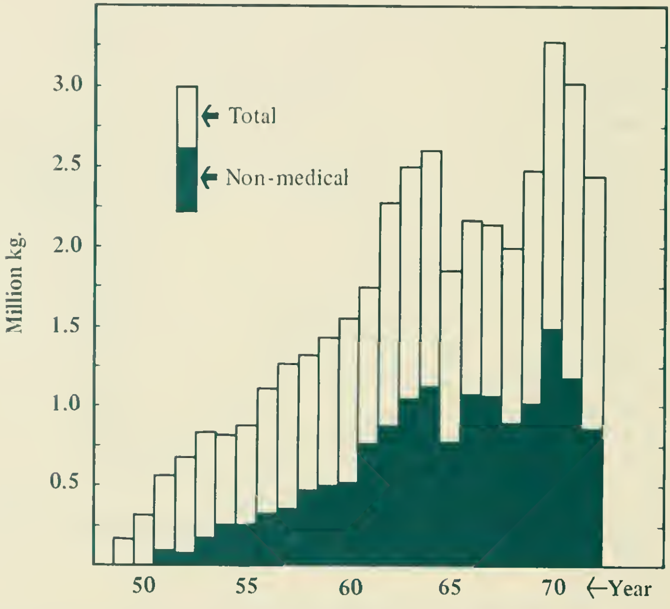


Figure 2. Sales of antibiotics for medical and nonmedical uses, 1949 to 1973 (536).

It is widely recognized that antibiotics effective in improving the performance of animals have one thing in common: the suppression or inhibition of the growth of certain microorganisms. Their chemical compositions and bacterial spectra vary widely. Some of the effective antibiotics are readilv absorbed into the vascular system;others are barely absorbed. The chemical compositions, bacterial spectra and absorption and excretion patterns of these products are clearly associated with their bactericidal and bacteriostatic properties and effectiveness against specific systemic infections; however, these characteristics are less readily associated with effectiveness as a routine growth promoter.

II. Mode of Action

For the growth-promoting activity of antibiotics, at least three modes of action have been postulated, each with varying degrees of support: (a) The metabolic effect: The antibiotics directly affect the rate or pattern of the metabolic processes; (b) The nutrient-sparing effect: The antibiotics may reduce the dietary requirement for certain nutrients by stimulating the growth of desirable organisms which synthesize vitamins or amino acids, by depressing the organisms which compete with the host animal for nutrients, by increasing the availability of nutrients via chelation mechanisms, or by improving the absorptive capacity of the intestinal tract; (c) The disease control effect: The suppression of organisms causing clinical or subclinical disease, by inhibition of multiplication of organisms that produce toxins, or by limiting their capacity to produce toxins which reduce performance but result in no obvious symptoms of disease.

A. Metabolic Effect

The data which support the metabolic effect theory also tend to support a disease-control effect, as the rate of metabolism may be influenced by systemic infections, digestive upsets or absorption of microbially-produced toxins from the gastrointestinal tract. Metabolic reactions are influenced by antibiotics: Braude and Johnson (65) reported that the feeding of chlortetracycline affected water and nitrogen excretion and suggested that it may influence the metabolic rate of pigs; Brody *et al*. (73), using rat liver homogentates, found that tetracyclines inhibited fatty acid oxidation by the mitochondria. Weinberg (571) also showed that, in bacteria, phosphorylation and oxidation reactions requiring magnesium ions were inhibited by tetracyclines; and, Hash *et al*. (207) demonstrated that tetracyclines inhibited protein synthesis.

Numerous reports illustrate that antibiotics have metabolic implications, and that bacteriostatic or bactericidal properties are associated with metabolic effects. However, in view of the nature of the animal responses, the normal tissue levels of the antibiotics when added to the diet at growth promoting levels and the levels necessary to mediate such biochemical responses, the metabolic effects cannot account for the growth promotion in animals fed diets supplemented with moderate levels of antibiotics. Furthermore, a direct metabolic effect should not vary greatly with the environmental conditions as discussed in the subsequent section on disease control effect. A direct metabolic effect could be consistent with variations discussed in the nutrient sparing section as nutrient levels at the site of metabolic reactions could modify rate and extent of metabolic reactions.

B. Nutrient Sparing Effect

The nutrient-sparing effect has considerable research support. It is well recognized that certain intestinal organisms synthesize vitamins and amino acids which are essential and that other bacteria require and compete with the host animal for these essential dietary nutrients.

Moore *et al*. (359) reported that streptomycin stimulated the growth or permitted rapid growth of some yeasts; Anderson *et al*. (8) found that feeding diets containing

penicillin increased the numbers of intestinal coliforms other than Escherichia coli. Such organisms synthesize nutrients that are dietary essentials; if a diet is deficient in a specific nutrient, this deficiency could be partially corrected by microbial synthesis and the specific nutrient subsequently made available for absorption by the host through digestion of the microorganism or by other means of release of the nutrient from the microorganism.

Other researchers report a depression in growth of organisms that are considered competitive with the host animals for dietary needs. March and Biely (315) indicated that the bacteria most affected by chlortetracycline were the lactobacilli. Anderson et al. (9) and Johansson and Sarles (258) also reported that antibiotics caused a reduction in the numbers of lactobacilli; Anderson et al. (9) reported that penicillin decreased the number of enterococci in the cecum of the chick. The lactobacilli require amino acids in relatively proportionally similar amounts as chicks and pigs; studies have shown that levels and sources of proteins which support maximum growth in pigs are also near optimum for the multiplication of lactobacilli in the intestinal tract (Kellogg et al. 273a). Hence the bacteria can compete with their host for essential amino acids not present or deficient in the diet. Though these bacteria may later be digested, the site of digestion may be past the site of optimal absorption. It has also been observed that those antibiotics most effective in reducing the number of these organisms in the intestinal tract, thus reducing competition for nutrients, are also the most effective as routine growth promoters (Kellogg et al. 272). A reduction in populations of organisms which compete with the host animal for the dietary essential nutrients may be beneficial, especially if the levels of certain essential nutrients are critically low. Such mechanism of action could partially explain the unusually marked responses reported for some experiments in the early 1950's, when optimum levels of many of the essential amino acids and vitamins were unknown.

Another type of nutrient sparing effect could be the improved utilization, particularly improved absorption, of the limited quantities of nutrients available to the host animal. Catron et al. (99) reported an increased rate of glucose absorption in animals fed rations fortified with antibiotics, thus providing evidence for the improved nutrient utilization by improvement of the absorptive capacity of the intestinal tract. Coates (110) demonstrated that the gut wall was thinner in chicks fed rations containing an antibiotic than the intestinal wall of chicks fed diets not containing antibiotics. Rusoff et al. (433b) and Braude et al. (64) observed similar effects in calves and pigs, respectively. Coates also noted that feeding chicks the intestinal contents of infected chicks resulted in a thickening of the intestinal wall. Similar effects of antibiotics on the thickness of the intestinal wall have been reported by others (Coates et al., 111; Gordon, 184, 185a; Gordon et al., 185b; Hill et al., 236; and Taylor and Harrington, 522). The thinner intestinal wall implies a potential for improved absorption (Taylor, 521) and is assumed to be a result of the inhibition of the organisms which produce toxins or of the production of toxins which damage intestinal tissue. Improved utilization of nutrients due to a healthier intestinal wall actually could be classed as reduction in subclinical disease or inhibition of toxin production.

Catron et al (98), Burnside et al. (83) and Beacom (30, 31) reported research which

suggested that the level of protein required by pigs for maximum performance was less in the presence of dietary supplements of antibiotics. Tables 1 and 2 summarize the response of pigs and chicks, respectively, to varying protein levels in the presence or absence of antibiotics and show that maximum gains may be obtained at a slightly lower level of protein if antibiotics are present in the diet or expressed differently; rate of gain is depressed more by low protein in the absence than in the presence of the antibiotic.

TABLE 1

EFFECT OF CHLORTETRACYCLINE ON WEIGHT GAINS OF PIGS FED PROTEIN AT FOUR LEVELS[a]

Protein Level Fed (%)	Average Daily Gain (g) Control	Average Daily Gain (g) Fed Chlortetracycline	Feed Efficiency[b] Control	Feed Efficiency[b] Fed Chlortetracycline
20-17-14[c]	690	760	3.90	3.54
18-15-12	708	754	3.83	3.60
16-13-10	740	760	3.72	3.55
14-11-8	681	754	3.74	3.59

[a]Catron et al. (98).
[b]Units of feed per unit of gain.
[c]Percent protein in the diet for the weight periods initial to 68, 34 to 68 and 68 to 91 kg. body weight, respectively.

TABLE 2

EFFECT OF ANTIBIOTICS ON THE RESPONSE OF CHICKS TO VARYING PROTEIN LEVELS[a]

Protein Level	Weight, g Controls	Weight, g Antibiotic	Weight, g Improvement	Feed/Gain Controls	Feed/Gain Antibiotic	Feed/Gain Improvement
%	g	g	%			%
16	977	1055	8.0	3.32	3.03	8.7
18	1058	1161	9.7	3.06	2.82	7.8
20	1133	1171	3.4	2.97	2.93	1.3
22	1097	1153	5.1	3.22	3.05	5.3
24	1123	1149	2.3	3.24	3.07	5.2

[a]Summary of 4 experiments, West and Hill (574).

The effect of protein level on response is more obvious in the chick data in Table 2. The optimum level of protein for chicks is about 20%. At or above that level,

chick weights were improved by 2.3 to 5.1%. Below that level, antibiotics improved chick weights by 8.0 to 9.7%. Note similar effects on feed/gain.

Not only is there an interaction of antibiotics and level of protein (provided the levels of protein tested include a definite sub-optimum level) but also there is an interaction of antibiotics and the quality (amino acid balance) of protein. For young calves and pigs, milk proteins are definitely superior to vegetable proteins because the former are more readily digested and have superior amino acid balance. An example of the antibiotic x protein quality interaction is provided by Hogue et al. (240); the amount of milk in the diet of young dairy calves influenced their response to antibiotics. Though the growth rate of the calves was higher on the higher levels of milk, the response to chlortetracycline was greater (11.3% versus 5.1%) on the poorer quality (low milk) diet (Table 3).

TABLE 3

EFFECT OF CHLORTETRACYCLINE ON GROWTH OF CALVES FED MILK AT TWO LEVELS[a]

	Daily/Gain	
Level of Milk Fed	Average (g)	Improvement (%)
Low		
Control	481	
Fed Chlortetracycline	534	11.3
High		
Control	527	
Fed Chlortetracycline	554	5.1

[a]Hogue et al. (240).

Such diet x antibiotic interactions are reported for other species as well. From a comprehensive summary of the effects of antibiotics on the performance of beef cattle, Burroughs et al. (84a) also noted that animals on diets which resulted in less rapid and efficient gains (lower quality or lower in available nutrients) showed a greater percentage response to chlortetracycline (Table 4).

TABLE 4

EFFECT OF CHLORTETRACYCLINE ON WEIGHT GAINS OF BEEF CATTLE FED HIGHER AND LOWER GAINING DIETS[a]

Diet and No. Comparisons	Daily Gain		Feed/Gain[b]	
	Average (kg)	Improvement (%)	Average	Improvement (%)
Higher gaining diets (34 comparisons)				
Control	1.057		10.34	
Fed Chlortetracycline	1.103	4.3	9.96	3.7
Lower gaining diets (31 comparisons)				
Control	.645		12.31	
Fed Chlortetracycline	.681	5.6	11.45	7.0

[a]Burroughs et al. (84a).

[b]Units of feed per unit of gain.

Lucas (304), Braude et al. (66, 67), Stokstad (502), Burnside et al. (81) and others presented evidence of an association between diet and antibiotic response. This relationship can be seen in the change in response to antibiotics over years in Table 5.

TABLE 5

RESPONSE OF PIGS TO ANTIBIOTICS DURING THE STARTER STAGE (PIGS WEIGHING LESS THAN 35 POUNDS AT START OF TEST)

	Number[a]			Wt., lb.[b]		ADG, lb.[c]			Feed/Gain[c]		
	Exp.	Reps.	Pigs	I	F	–	+	% Imp.	–	+	% Imp.
Tetracyclines[d]	59	234	1654	17	53	.83	.92	10.84	2.24	2.10	6.25
Bacitracin[e]	11	54	228	15	43	.72	.79	9.72	2.15	2.08	3.26
Tylosin[f]	21	124	878	18	51	.81	.93	14.81	2.32	2.18	6.03
Penicillin-Streptomycin	40	95	545	25	73	1.01	1.16	14.85	2.56	2.37	7.42
Virginiamycin[h]	23	90	629	23	68	1.00	1.11	11.00	2.39	2.27	5.02
Bambermycins[i]	5	24	128	11	30	.53	.53	0.00	2.03	2.05	-0.99
Penicillin[j]	7	14	57	13	40	.74	.81	9.45	2.19	2.00	8.68
Chlortetracycline-Sulfamethazine-Penicillin[k]	78	302	2507	18	52	.78	.96	23.07	2.22	2.03	8.56
Chlortetracycline-Sulfathiazole-Penicillin[k]	9	31	292	22	61	.93	1.11	19.35	2.40	2.20	8.33

continued

	Number[a]			Wt., lb.[b]		ADG, lb.[c]			Feed/Gain[c]		
	Exp.	Reps.	Pigs	I	F	—	+	% Imp.	—	+	% Imp.
Tylosin-Sulfamethazine[l]	17	76	482	20	51	.85	1.00	17.65	2.07	1.93	6.76
Carbadox[m]	82	292	2195	21	60	.97	1.15	18.56	2.43	2.22	8.64
Lincomycin[n]	3	8	52	27	110	1.35	1.50	11.11	2.51	2.32	7.57
Nitrofurans[o]	23	66	376	23	83	1.00	1.08	8.00	2.57	2.51	2.33
Sums	378	1410	10,023								
Weighted avg.				19	57	.87	1.01	16.09	2.32	2.16	6.90
Tetracyclines:											
1950-1956	6	16	104	15	50	.92	1.00	8.70	2.20	2.08	5.45
1957-1966	38	128	863	15	50	.77	.86	11.69	2.27	2.09	7.93
1967-1977	15	90	687	24	61	.94	1.04	10.63	2.18	2.13	2.29

[a]Number of experiments and number of replications (pens) and pigs per treatment.

[b]Initial and final weight, lb.

[c]Average daily gain and feed/gain for pigs fed diets without (-) and with (+) antibiotics

[d]Chlortetracycline and oxytetracycline. References: 22, 23, 36, 55, 79, 98, 102, 107, 108, 127, 129, 147, 159, 216, 218, 220a, 242, 257, 259, 277, 294, 313, 426, 470, 494.

[e]References: 28, 108a, 123, 129, 257, 294.

[f]References: 32, 33, 129, 147, 247, 257, 277, 284, 298, 398, 434, 494, 538.

[g]Penicillin-Streptomycin. References: 34, 35, 36, 55, 68, 108, 147, 255, 257, 350, 398, 408, 427, 494, 540, 543, 553.

[h]References: 3, 125b, 129, 147, 257, 285, 343, 347, 348, 395, 396, 424, 434.

[i]References: 277, 494.

[j]References: 494.

[k]Chlortetracycline, Sulfamethazine or Sulfathiazole, Penicillin. References: 3, 4, 103, 104, 108, 147, 157a, 157b, 159, 161, 200, 201, 202, 203, 217, 219, 238, 259, 277, 280, 284, 313, 333, 334, 341, 375, 386, 390, 398, 455, 494, 529b, 532, 546, 550, 551, 552, 589.

[l]Tylosin-Sulfamethazine. References: 108, 247, 333, 334, 335, 341, 386, 436, 494, 529b.

[m]References: 3, 4, 126, 147, 157a, 198, 201, 219, 341, 369, 385, 386, 390, 398, 435, 529b, 531, 532, 546, 549, 552.

[n]References: 3, 199.

[o]References: 4, 20, 23, 24, 27, 108, 238, 425, 551, 552, 549.

In the 1950's most of the research with young pigs involved diets containing relatively high levels of milk products. In more recent years, much of the research effort has been devoted to improving performance on diets without milk, since milk is considered too expensive to use extensively in pig starters. Thus, while no change or a decrease in the response to antibiotics can be expected a higher level of response in the starter stage since 1957 than prior to 1957 is seen. The response to antibiotics is generally greater if the antibiotics are included in an inadequate diet. This response suggests an improved utilization of nutrients at critical or suboptimal levels and can be ascribed to nutrient synthesis by intestinal organisms, reduced competition from bacteria for critical nutrients or improved absorption.

Though there is substantial evidence that antibiotics will markedly enhance the performance of animals fed a diet low in protein or inadequate in other nutrients, there is evidence that the effect on nutrient utilization is indirect. Meade and Forbes (332), Wallace et al. (565) and Bush et al. (84b) presented evidence suggesting that enhancement in growth was accompanied by an increase in food intake; and though total nitrogen, calcium or other nutrients retained was greater, the percentages retained by the two groups of animals (those fed antibiotics and those not fed antibiotics) were similar. The increased feed intake accompanying response to antibiotics may provide evidence that the response is not a result of a direct effect on nutrient absorption or utilization; however, such evidence does not detract from the practical benefits of antibiotics. The improved feed intake may simply be a result of improved health resulting in improved growth rate and appetite, thus leading to improved efficiency. Environmental conditions existing in most balance studies (extreme cleanliness, one animal per metabolism crate, controlled temperature, etc.) are not conducive to dramatic antibiotic responses. Studies performed in more practical conditions in which feed intake was limited to a standard level, as practiced in Europe, have shown that responses to antibiotics occur even though feed intake is held constant. Data summarized by Melliere (336) illustrated that pigs fed at a restricted level responded to tylosin (Table 6).

TABLE 6
RESPONSE TO TYLOSIN IN PIGS FED A RESTRICTED AMOUNT OF FEED PER DAY[a,b]

Item	Controls	Plus Tylosin 22-44 ppm	Improvement %
No. replications	93	86	
Pigs per treatment	876	839	
Avg. daily feed intake, g	1958	1938	
Avg. daily gain, g	597	625	4.69
Feed/gain	3.31	3.13	5.44

[a]Melliere, 336.

[b]Results of trials on commercial farms in Germany, England, Holland and Italy.

In the United States growing pigs, chicks and turkeys are normally allowed ad libitum access to food.

The increased response to antibiotics in the presence of nutritional stresses is of major economic significance in the production of meat, milk and eggs, since it is often economically desirable or pragmatically convenient to feed nutrient sources or levels which will not promote maximum rate of gain. In livestock and poultry feeding programs, antibiotics may partially bridge the gap between optimum and economically practical diets. More specifically, protein supplies may be too expensive (as in the example of milk in pig starter diets) to permit the feeding of optimum levels. Feed quality may also vary depending on growing, harvesting or storage conditions. Such variations are beyond the control of livestock producers and cannot be entirely corrected by diet formulation.

C. Disease Control Effect

Though there is extensive evidence of nutritive and antibiotic response relationships, such effects appear secondary to the disease-control effect. Numerous studies support the conclusion that the major benefits derived from antibiotics as routine feed additives result from the suppression or control of subclinical or nonspecific diseases. Early in the history of antibiotics as supplements to animal feeds, it was noted that the degree of response to antibiotics was inversely related to the general well-being of the experimental animals. Speer et al. (497) observed that healthy, well-nourished pigs did not respond to antibiotic supplements when housed in carefully cleaned and disinfected pens which had not been previously used. These findings have been confirmed by other research with other species (Catron et al., 100; Coates et al., 112 and Hill et al., 234).

Studies involving both clean and contaminated environments illustrated that the response was greater in contaminated or previously used environments. Bowland (56) presented results of pig tests involving a new and an old barn. His data, summarized in Table 7, show that antibiotics resulted in a 14.3% increase in growth rate of pigs housed in the old barn; in the new barn, antibiotics resulted in only a 7.5% increase in growth rate.

TABLE 7

EFFECT OF CHLORTETRACYCLINE ON WEIGHT GAINS OF PIGS IN DIFFERENT ENVIRONMENTS[a]

Environment and Chlortetracycline Fed	Daily Gain		Feed Efficiency[b]	
	Average (g)	Improvement (%)	Average	Improvement (%)
New barn				
Control	604		4.15	
Chlortetracycline (9 g/ton)	649	7.5	3.92	5.5
Old barn				
Control	604		4.21	
Chlortetracycline (9 g/ton)	690	14.2	3.78	10.2

[a]Bowland (56).

[b]Units of feed per unit of gain.

Similar differences were noted for improvements in feed conversion in the new and old barns. Bird et al. (48) presented similar results with chicks. The response of chicks to chlortetracycline in a new environment was 12.6% improvement in gains during four weeks, as compared to 18.2% for chicks from the same hatch that were reared in the previously used environment (Table 8). Coates et al. (112) reported similar observations (Table 8).

TABLE 8

RESPONSE OF CHICKS TO CHLORTETRACYCLINE (CTC) AND PENICILLIN IN NEW AND PREVIOUSLY USED ENVIRONMENT

Environment	Treatment	4 wk. Wt. (g)	Improvement (%)
Bird, et al., 48			
New house	Control	254	
	CTC, 10 ppm	286	12.6
Previously used house	Control	176	
	CTC, 10 ppm	208	18.2
Coates, et al., 112[a]			
Greenford Lab.	Control	184	
	Penicillin	187	1.6
Reading Lab.	Control	155	
	Penicillin	192	23.9

[a]Reading Lab. had been previously used to house chicks but the Greenford Lab. had not.

In a previously used environment, penicillin increased gains by 23.9%; gains were improved by only 1.6% in the unit not previously used.

Wachholz and Heidenreich (538) provided additional evidence that the cleanliness or previous use of the environment affected the magnitude of the response to antibiotics (Table 9).

TABLE 9

RESPONSE TO TYLOSIN BY PIGS HOUSED IN TWO ENVIRONMENTS - NEW BARN VS. DIRT LOTS[a]

Environment	New House			Dirt Lots[b]		
Tylosin[c]	0	+	Improvement (%)	0	+	Improvement (%)
ADG, kg.						
Starter	.55	.63	14.6	.42	.50	19.0
Grower	.84	.82	2.4	.58	.68	17.2
Finisher	.95	.99	4.2	.73	.80	9.6
Feed/gain						
Starter	2.48	2.29	7.7	2.74	2.53	7.6
Grower	2.53	2.56	4.2	3.19	2.94	8.0
Finisher	3.15	3.15	0.3	3.70	3.52	4.9

[a]Wachholz and Heidenreich (538).

[b]Area had been used several years for rearing pigs.

[c]110, 44 and 11mg/kg., respectively for starter, grower and finisher diets.

They tested the growth promoting effects of tylosin in a new barn and in a dirt lot facility which had been used for pigs for several years. The increased rate of gain from supplementing the diet with tylosin averaged 2.4 to 14.6% in the new barn as compared with 9.6 to 19% in the dirt lot facility, a less desirable environment. Obviously new buildings cannot be provided for each batch of chicks or pigs, but such data illustrate the need for improved sanitary practices.

Hays and Speer (216) conducted two field tests comparing the effectiveness of different levels of spiramycin (Table 10).

TABLE 10

EFFECT OF SPIRAMYCIN AND TETRACYCLINES ON WEIGHT GAINS OF PIGS FED IN TWO ENVIRONMENTS[a]

Environment and Level of Spiramycin Fed	Total Gain		Feed Efficiency[b]	
	Average kg.	Improvement (%)	Average	Improvement (%)
First environment[c, d]				
No antibiotic	8.13		1.90	
12.5 g/ton	9.62	18.3	1.84	3.2
25 g/ton	10.44	28.4	1.64	13.7
50 g/ton	10.81	33.0	1.70	10.5
Tetracycline[e]	10.71	31.7	1.78	6.3
Second environment[f, g]				
No antibiotic	4.81		2.89	
12.5 g/ton	6.13	27.4	2.40	17.0
25 g/ton	7.99	66.1	1.95	32.5
50 g/ton	8.40	74.6	1.83	36.7
Tetracycline[e]	7.35	52.8	2.03	29.8

[a] Hays and Speer (216).

[b] Unit of feed per unit of gain.

[c] Building thoroughly cleaned and disinfected before test, occupied only by pigs in test.

[d] 64 pigs fed at each level, averaging 26.3 days of age and 5.63 kg. body weight, initially.

[e] 50 g/ton of chlortetracycline or oxytetracycline in first and second environments, respectively.

[f] Building not thoroughly cleaned before test and contained older pigs before and during test.

[g] 59 pigs fed at each level, averaging 31.8 days of age and 5.69 kg. body weight, initially.

In one test, the building was emptied, thoroughly cleaned and disinfected before starting the test, and only those pigs involved occupied the building during the test. The building used in the other test contained older pigs preceding and during the test, and neither the building nor the individual pens were thoroughly cleaned or disinfected before the test. In the cleaner environment, spiramycin (50 g/ton of diet) resulted in a 33% improvement in gains and a 10.5% improvement in feed efficiency; in the uncleaned building, the addition of the same level of antibiotic to the diet resulted in a 75% increase in growth rate and a 37% improvement in feed conversion. Similar responses to chlortetracycline (50 g/ton) and to oxytetracycline (50 g/ton) were noted.

Lower levels of spiramycin resulted in lower response. Though other variables, such as climatic conditions and breeding of animals, may have influenced the performance, the relative contamination of the buildings obviously had an important bearing on response to antibiotics. The buildup of a nonspecific infection in buildings continuously used to house animals can depress performance of animals without resulting in obvious symptoms of a disease problem. This is the kind of problem for which routine feeding of antibiotics is useful and therapeutic use is not indicated.

Scott (449) presented an excellent example of the buildup of the growth depressing effect of non-specific infections in a chick starting facility. The performance of successive hatches of chicks of similar breeding and fed similar diets was poorer than that of previous hatches (Table 11).

TABLE 11

EFFECT OF A "NON-SPECIFIC INFECTION" ON CHICK GROWTH[a]

Hatch No.	Avg. Gain 0-7 Days	Relative Gain
	(g)	(%)
1	44.2	100.0
2	42.7	96.6
3	41.5	93.9
4	40.1	90.7
5	42.8	96.8
6	41.8	94.6
7	40.9	92.5
8	40.2	91.0
9	39.5	89.4
10	35.2	79.7
Depopulation and fumigation		
11	37.7	85.3
12	26.2	59.3
Depopulation and fumigation		
13	38.2	86.4
14	34.5	78.1
15	28.3	64.0

[a]Adapted from Scott, 449.

Emptying the facility, cleaning it thoroughly and fumigating it resulted in some improvement in performance. However, even this did not result in a growth rate of chicks approaching the level of performance of the first hatch. These are the kinds of problems which feed additive usage of antibiotics help to control. Some critics of antibiotic usage have suggested that the only need for antibiotics results from housing pigs and chicks in filthy overcrowded houses. Such statements are greatly exaggerated and suggest that the individuals are not acquainted with practical livestock and poultry production. Even in the new house illustrations above, there were responses to antibiotics. Furthermore, the most uninformed should recognize that new facilities or complete isolation cannot be afforded for each farrowing of pigs or hatch of chicks.

The challenge experiments of Miyat and Gossett (353) further demonstrated the prophylactic effects of antibiotics in controlling specific diseases (Table 12).

TABLE 12

EFFECT OF FEEDING TYLOSIN ON EXPERIMENTALLY INDUCED HEMORRHAGIC DYSENTERY IN PIGS[a]

Amount of Tylosin Fed		No. Pigs at		Average Weight (kg)		
In Water	In Feed g/ton	Start of Trial	End of Trial	Initial	Final	Feed Efficiency[b]
TRIAL 1						
0	0	24	12	16.66	37.82	20.6
250 mg/gal[c]	40[d]	23	23	16.57	57.52	2.85
250 mg/gal[c]	0	23	20	16.66	47.31	3.84
0	100[e]	24	23	16.57	62.97	2.82
TRIAL 2						
0	0	23	13	35.96	59.02	
250 mg/gal[c]	40[d]	21	19	35.32	64.65	4.20
250 mg/gal[c]	0	22	20	36.37	63.97	4.90
0	100[e]	23	18	35.90	67.28	5.86

[a]Miyat and Gossett (353).

[b]Units of feed per unit of gain.

[c]Antibiotic included in water for 6 to 8 days before infection and for 4 or 5 days after infection.

[d]40 g/ton of feed after water treatment

[e]100 g/ton of feed for 2 days before and for 33 or 15 days after infection, followed by 40 g/ton.

Treatment with tylosin was effective in controlling hemorrhagic dysentery, but treatment followed by prophylactic administration of the antibiotic was more effective in restoring performance to normal. These data illustrate the marked improvement in performance resulting from antibiotic supplements in severely high and, in this case, specific disease conditions. Similar observations have been reported on naturally occurring outbreaks of hemorrhagic dysentery (Gossett and Miyat, 186).

Braude et al. (67) summarized a large number of experiments and concluded that the relative improvement in growth rate resulting from supplementing the diets with antibiotics was inversely related to the growth rate of the control animals (Table 13).

TABLE 13

RELATIONSHIP BETWEEN GROWTH RATE OF CONTROL ANIMALS AND ANIMALS FED ANTIBIOTICS[a]

	Daily Gain in Weight (g)		Response to
No. of Tests	Control Animals	Antibiotic-Fed Animals	Antibiotic: Improvement (%)
4	94	245	161
1	136	227	67
12	182	336	85
13	227	340	50
16	272	449	65
31	318	481	51
12	363	499	38
18	409	563	38
16	454	572	26
36	499	572	15
32	545	627	15
39	590	636	8
48	636	713	12
20	681	735	8
22	726	790	9
1	772	881	14

[a]Adapted from Braude et al. (67).

Similar experiments, involving the antibiotic combination of penicillin and streptomycin and conducted about ten years after the studies by Braude et al. are summarized and presented in Table 14.

TABLE 14

RELATIONSHIP BETWEEN GROWTH RATE OF CONTROL PIGS AND PIGS FED A COMBINATION OF PENICILLIN AND STREPTOMYCIN[a]

Daily Gain In Weight of Controls (g)	No. of Comparisons	Improvement Over Controls By Pigs Fed Antibiotics	
		Gain in Weight (%)	Feed Efficiency (%)
91 to 182	2	22.0	8.2
182 to 272	3	27.0	4.5
272 to 363	4	20.4	5.6
363 to 454	7	16.1	11.1
454 to 545	9	12.3	6.4
545 to 636	9	9.4	1.9
636 to 726	20	5.6	4.7
726+	7	3.8	1.8
Total	61		
Average Improvement, %		10.7	5.1

[a]Data summarized from agricultural experiment station reports, 1960 to 1967 (212a).

Of 61 comparisons included in the summary, 56 showed a positive response in feed conversion, with average improvements of 10.7% and 5.1% for rate of gain and feed efficiency, respectively.

As mentioned earlier, the observation that degree of response is associated with degree of contamination has led to the suggestion that antibiotics are being used as a substitute for good housekeeping and sanitation procedures. There are practical and economic limits which can be made by livestock producers in sanitation procedures. Experiment stations, which usually employ husbandry and sanitation practices beyond the practical limits of producers, do, nonetheless, note responses to antibiotics of substantial magnitude.

The data used to estimate the economic benefits from the use of antibiotics are for the most part based on experiments conducted at experiment stations. Most of the

data used in estimating benefits to poultry is based on performance of chicks in batteries. Experiment station researchers employ management and sanitation procedures that are difficult, or nearly impossible, and certainly often impractical for the producer. For example, many of the tests involve only healthy pigs at the beginning; however, the farmer must rear all of his pigs. The exaggerated response to antibiotics by unthrifty (runt) pigs is illustrated by a number of experiments, some of which are summarized in Table 15.

TABLE 15.

VALUE OF CHLORTETRACYCLINE FOR UNTHRIFTY PIGS[a]

	As Percent of Controls	
Exp.	ADG	F/G
1	203	79
2	184	79
3	315	63
4	215	76
5	121	87
6	151	86
7	186	78
8	161	86
9	149	83
10	173	69
11	300	71
Avg.	196	77

[a]Braude et al. (67).

Researchers normally cull out this quality of pigs prior to starting the experiments. Note that antibiotics resulted in a near doubling of the growth rates and improved feed efficiency by an average of 77%. These studies are included in the upper part of Tables 13 and 14. Sainsbury (439) also presented an excellent example of the difference in response of normal healthy pigs and those he classed as "bad doers" or what we frequently term as "runt" or "unthrifty" pigs. Antibiotic supplements

to the diet of the normal pigs resulted in a 10% improvement in rate of gain; antibiotic supplements to the "bad doers" resulted in a 30% improvement in gains. Thus, if unselected pigs are used (as the producer must), a greater response to antibiotics is expectable than if only healthy pigs are selected.

Also, researchers usually clean the facility well and the facility may be idle between groups of pigs or chicks. This practice should result in a lesser response to antibiotics as illustrated in Table 10. It is difficult or nearly impossible to thoroughly clean and sanitize many swine facilities.

Another procedure commonly followed in many experiments which undoubtedly reduces the stress on animals and hence reduces the expected response to antibiotics is the practice of using only a few animals per pen. In fact, some of the antibiotic studies involve single pigs per pen; most involve only 4 to 6 animals per pen. It is obvious that this is not a practical management procedure. It is common practice to have 75 to 100 or more pigs per pen. Many chick and turkey experiments involve 10 or fewer birds per pen and often in wire floored batteries; in practical production, hundreds may be housed per pen.

Melliere et al. (338) summarized 69 swine experiments conducted under research station and farm conditions and verifies that the average response is greater in the farm situation. Their data are reported in more detail by Natz (374) and summarized in Table 16.

TABLE 16.

EFFECT OF TYLOSIN ON GROWTH RATE AND FEED CONVERSION OF FINISHING PIGS[a]

		Treatment		
Experimental Unit	Trials	Control	Tylosin 10-20	Improvement
Average daily gain	No.		g/day	%
Research type 1[b]	32	790	803	1.7
Research type 2[c]	22	763	790	3.6
Field tests[d]	24	713	754	5.7
Avg.		755	783	3.7
Feed/gain			feed/gain	
Research type 1[b]	32	3.36	3.35	0.3
Research type 2[c, e]	16	3.64	3.52	3.3
Field tests[d]	24	3.84	3.66	4.7
Avg.		3.61	3.51	2.8

continued

[a] Melliere (338) and Natz (374).

[b] Closed herds, confinement houses thoroughly cleaned prior to test.

[c] Herd status and cleaning procedures not defined.

[d] Practical production units.

[e] Feed/gain data available on only 16 of the 22 experiments for which rate of gain data were available.

The average response for rate of gain and feed/gain was 5.7 and 4.7, respectively in field trials as compared with 3.6 and 3.3 for University Experiment Station tests. In experiments carried out in facilities in which extreme care was taken to maximize sanitary conditions, the response was 1.7 and 0.3% improvement in gain and feed/gain, respectively. Table 17 also presents a summary of differences in response to antibiotics in practical and experiment station environments, summarized from the observations included in Table 5.

TABLE 17

RESPONSE TO ANTIBACTERIALS (STARTER PIGS)[a]

	% Improvement	
Location	A.D.G.	F/G
32 Field tests	28.4	14.5
128 Exp. Sta. tests	16.9	7.0

[a] Summarized from data included in Table 5 and based on experiments involving 12,000 pigs. The antibacterials tested include tetracycline, tetracyclines in combination with penicillin and sulfamethazine, carbadox and the combination of tylosin and sulfamethazine.

Note that in field conditions the response to antibacterial agents is nearly double that observed for experiment station conditions. Thus, if the economic benefits are calculated from the use of antibiotics on data from experiments in the field, rather than from experiment station data, such benefits would greatly exceed the 533 million dollar estimate of Gilliam and Martin (181) for economic returns to use of antibiotics in swine production.

It has been suggested that there is no need for feed additive usage of antibiotics if one has a Specific-Pathogen-Free (SPF) or Minimal Disease (MD) herd. SPF and MD are terms used in the U.S. and Great Britain, respectively, to designate animals that are free of mycoplasma pneumonia, atrophic rhinitis and possibly other diseases that are spread by direct pig to pig contact. Any reduction in disease should lower the response to antibiotics. However, there are many experiments which illustrate that SPF pigs respond to antibiotics. Much of the data available has been summarized by Hays (211), and indicates that there is little difference in responses to antibiotics by SPF and non-SPF pigs used in experiment station research. Sainsbury (439) also reported that MD pigs fed antibiotic supplemented diets grew 8% faster than their respective controls as compared with a 10% improvement for conventional pigs supplemented with antibiotics. Every practical method should be utilized to reduce the morbidity and mortality from disease; however, at present there are no methods available that would contraindicate the need for feed additives. The wise use of antibiotics is not a substitute for but complements good husbandry, sanitation and disease control practices.

III. Continued Effectiveness

The extensive use of antibiotics as feed additives has elicited concern about potential harmful effects due to the development of resistant strains of organisms in the host animal or due to resistant organisms or allergic reactions in the consumer of the meat, milk or eggs from animals continuously fed antibiotics. Concern should exist with the application of any new drug either as a feed additive or a medicament; but, after 27 years of usage of some of these drugs, fear should have changed to rational thinking leading to adequate evaluation of the potential harmful effects as contrasted with the proven health and economic benefits.

After more than 27 years of extensive use of antibiotics in animal feeds, discussions still deal with "potential" public health hazards, as did a presentation 16 years ago (Goldberg, 183). Significantly, it is difficult to cite a single human health problem that can be attributed to the consumption of meat from animals fed antibiotics or that can be associated with direct or indirect contact with animals fed antibiotics.

It has been well established that continuous exposure of enteric organisms to an antibiotic permits the development of strains of organisms with greater tolerance for or complete resistance to that antibiotic. This is more readily demonstrated in laboratory tests (in vitro) with pure cultures than it is with the complex microflora which exists in the environment or in the gastrointestinal tract of domestic animals. However, an increase in multiple and transferrable drug resistance has been observed in naturally occurring enteric organisms from the use of antibiotics as feed additives (Smith et al., 485, and others).

The evidence that resistant organisms in animals compromise treatment of diseases in man or animals is indirect and difficult to evaluate. For those persons concerned only with disease treatment, the idealistic decision is to strictly limit the use of any drug to

treatment of a patient now or a "potential" patient in the future. For those who are concerned with a healthy population and a plentiful food supply, which involves both disease protection and efficient food production, the decisions are more complicated. A thorough evaluation of the human health implications of any biologically active drug is essential. When there are benefits, that is when there is some biological activity, there are likely to be some risks involved. A more thorough discussion of the risks or potential risks of feed additive usage is covered in other papers.

It has been suggested that antibiotics are losing their effectiveness and that ever higher levels are being required to give the typical antibiotic response. The general explanation for this is that the problem organisms are developing or have developed resistance to the antibiotics. It is recognized today that 40 to 50 g/ton of a broad spectrum antibiotic is normally required to approach a maximum response, whereas the generally recommended level in the 1950's was 10 to 20 g/ton. However, the data of Catron et al. (100) illustrate that, since antibiotics were first used, the recommended feeding level has not necessarily been the level which would elicit maximum response. Even though a response was obtained with 10 to 20 g/ton (Table 18), maximum gain was approached at 40 g/ton, and maximum feed efficiency was realized only at 80 g/ton, the highest level tested.

TABLE 18.

EFFECT OF CHLORTETRACYCLINE FED AT DIFFERENT LEVELS ON PERFORMANCE OF GROWING-FINISHING SWINE[a]

Level of Chlortetracycline (g/ton)	Average Daily Gain (g)	Feed Consumed Per Day (g)	Feed Efficiency[b]
0	654	2343	3.69
10	722	2443	3.49
20	726	2479	3.50
40	758	2588	3.44
80	763	2561	3.36

[a] Catron et al. (100).

[b] Feed required per unit gain.

Braude, et al. (67) reported in 1953 that more than 20 g/ton of tetracycline or penicillin was required for maximum response. Excluding experiments involving inadequate diets

or runt pigs, the percentage responses to tetracycline were 15.2 and 18.6 and to penicillin were 9.1 and 13.1 for below and above 20 g/ton, respectively. These observations were based on 125 tetracycline experiments and 45 penicillin experiments.

The levels selected for practical use are not necessarily the levels that will elicit maximum response. The growth response increases with increasing levels of antibiotics, up to 250 g/ton or more in some cases. The rate of increase in growth response decreases, however, as the level of antibiotic increases; thus, the level selected in practice is usually a compromise based on the cost-benefit ratio.

Improved methods of producing antibiotics and competition among producers have resulted in a decline in the price of the commonly used antibiotics, which allows consideration of the use of higher levels. Figure 1 presents price data for all antibiotics combined and Table 19 presents the specific price histories of penicillin, streptomycin and tetracyclines.

TABLE 19.

APPROXIMATE PRICE PER KILOGRAM OF FEED-GRADE ANTIBIOTICS FOR THE SPECIFIED YEARS, 1950-1975

Year	Penicillin	Streptomycin	Tetracyclines
1950	$ 200	$ 200	$ 120
1955	50	55	100
1960	22	30	80
1965	20	20	60
1970	24	28	30
1975	26	29	22

The prices of feed-grade penicillin and streptomycin in 1975 were only 10 to 15% of the 1950 price and tetracyclines were only about 20% as expensive as in 1950. These reductions in antibiotic prices were accompanied by increases in most other production costs. The evidence available suggests that the decrease in cost of antibiotics per gram and the increase in other production costs have been the primary reasons for higher levels being recommended and used rather than any decline in effectiveness. The higher levels were more effective from the beginning; but, with the natural biological phenomena of a decreasing rate of increase with an increasing level, the practical optimum level changes with cost changes, not only of the antibiotics, but other production costs and in addition change with the market prices received for pigs. Prices of certain antibiotics have increased within the past five years. These have essentially attained basic commodity

status (patent protection is gone for the older ones) and prices will respond to ingredient, labor, transportation and other routine production costs. Removal of the older antibiotics from use in livestock production will increase cost of production, as it will force the use of drugs that still are covered by patent protection in addition to removing some of the most effective in terms of improving rate and efficiency of gain.

Certainly, there are tests in which little or no response is observed to a recommended level of an antibiotic. This situation is not peculiar to the present. Similar observations have been reported since the early use of antibiotics as dietary supplements. Speer et al. (497) reported that 10 to 20 g of chlortetracycline per ton of diet did not improve the performance of pigs in one test and suggested that the low disease level could be the reason for lack of improvement.

Teague et al. (523) reviewed the antibiotic studies conducted at the Ohio Station between 1950 and 1963. Variations were noted in the response from year to year, but there was no consistent decline in antibiotic response. A similar study of the swine data from the Iowa Station, 1950 - 1959, suggests that less response to antibiotics existed (Figure 3) during 1953-1956.

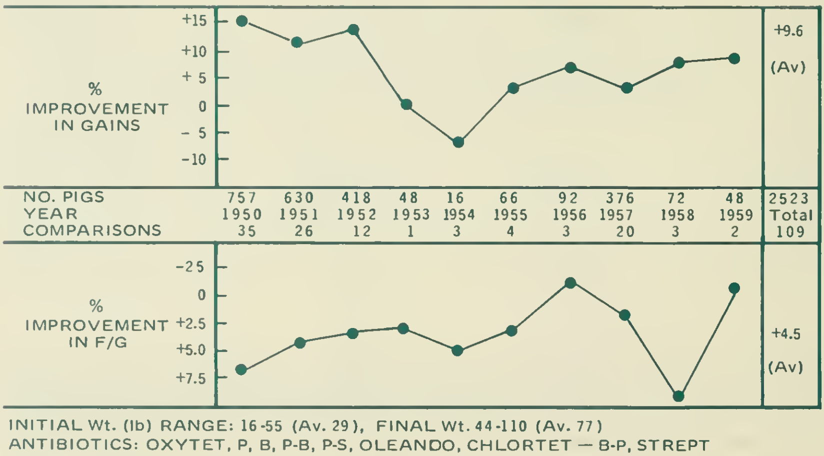


Figure 3. Response of growing pigs to antibiotics (V. C. Speer, Animal Science Department, Iowa Agric. and Home Econ. Exp. Sta.)

A critical evaluation of the experiments conducted during those years shows that few were performed and usually involved individually fed pigs in experiments designed to study the effects of antibiotics on protein or vitamin utilization. The disease stress on the animals was thus minimized as most of the animals were individually penned in metabolism cages.

Peo (397) summarized the long-term effects of antibiotic feeding to swine at the Nebraska Station and concluded that, after more than ten years of extensive use of antibiotics, a response was still being observed. His observations are particularly relevant, since, in that period of time, the Nebraska researchers had changed to a "specific pathogen-free"herd and had strived to keep disease conditions at a minimum.

Hvidsten and Homb (250) reported the results of 9 consecutive experiments on one farm in which oxytetracycline and chlortetracycline were tested at low or high levels. The antibiotic-fed pigs gained 5% faster on the average for the 9 trials and the average improvement for the 9th trial was 5.3%. The lowest response to antibiotics was observed in the 4th trial and the highest in the 5th trial, suggesting that the variations in results was largely a result of normal variation associated with small experiments, and not a reflection of a changing response to antibiotics.

To evaluate the continued effectiveness of tetracycline and the combination of tetracycline, penicillin and sulfamethazine, the data in Table 5 were statistically analyzed. The differences between control and treated groups were highly significant ($P<.01$) for average daily gain and feed required per pound of gain, for both the tetracycline experiments and the experiments involving the antibiotic combination. For the tetracycline experiments the predicted difference was 0.10 lb/day increase in rate of gain and a reduction of 0.12 lb. of feed per pound of gain as a result of having the antibiotic in the diet. There was no evidence of a reduced effect with successive years of use. The predicted improvements in rate of gain and feed conversion were 11.3% and 4.6%, respectively, as compared with the observed values of 10.8% and 6.2%. The predicted differences were adjusted to a common initial weight (17.4 lb.) and equal time on experiment (40.4 days).

For the experiments involving the combination of antibiotics, there was evidence of a year by treatment interaction. A plot of the data showed an improvement with time in rate of gain for the controls followed by a leveling or dropping off, with little or no change in the performance of the treated group. The difference between controls and the treated group was highly significant ($P<.01$). There was no evidence of a year by treatment interaction for feed/gain ratios with a constant difference of 0.17 lb. less feed per pound of gain for the treated group. The predicted improvement in feed conversion was 7.6% as compared with the observed average of 8.5% in Table 5. The predicted values are adjusted to equal initial weights (18.4 lb.) and to equal time on experiment (36.2 days).

The statistical analysis of each of these sets of data supports the conclusion that tetracycline or the combination of tetracycline, penicillin and sulfamethazine is still effective in improving performance, with little or no evidence of a decline in effectiveness with time.

Similar questions have been raised about the continued effectiveness in poultry. Bird (46) summarized data from 1951 to 1968 on birds taken from hatching to broiler weights

and concluded that the trends did not indicate a decrease in effectiveness. Table 20 presents a series of trials from 1964 to 1976 in which penicillin was used as a standard in screening tests (Kiser, 273b).

TABLE 20

SUMMARY OF CHICK RESPONSE TO PENICILLIN[a]

Year	No. of Expts.[b]	Birds Fed Basal Diet		Birds Fed Penicillin in Diet[c]		% Improvement over Basal	
		Gain (g)	F/G	Gain (g)	F/G	Gain ± S.E.M.	F/G ± S.E.M.
1964	11	250	1.76	294	1.56	17.5 ± 1.71	11.3 ± 1.66
1965	23	289	1.64	324	1.52	12.1 ± 0.87	6.9 ± 0.58
1966	43	291	1.63	330	1.50	13.4 ± 0.68	7.8 ± 0.48
1967	23	267	1.69	311	1.52	16.6 ± 1.01	9.5 ± 0.70
1968	38	262	1.64	301	1.53	15.0 ± 1.03	6.9 ± 0.61
1969	39	266	1.60	310	1.45	16.4 ± 0.86	8.2 ± 0.54
1970	30	271	1.58	310	1.45	14.3 ± 0.88	8.1 ± 0.47
1971	12	316	1.54	357	1.43	13.0 ± 2.19	7.4 ± 1.15
1972	24	193	1.47	211	1.37	9.3 ± 1.36	6.8 ± 0.76
1973	24	183	1.49	203	1.39	10.8 ± 0.72	6.5 ± 0.47
1974	44	189	1.45	207	1.36	9.7 ± 0.68	6.1 ± 0.48
1975	44	188	1.47	202	1.40	7.6 ± 0.37	5.3 ± 0.22
1976	36	190	1.47	206	1.39	8.5 ± 0.71	5.3 ± 0.56

[a]Kiser, 273b.

[b]Each experiment contained 2 replicates of 10 birds each (5 males, 5 females). Trial lengths were 20 days for 1964 to 1967, 19 days for 1968 to 1971 and 13 days for 1972 to date.

[c]Penicillin was present at 180 g/ton of diet.

After 12 years of continuous testing in the same laboratory, penicillin still results in substantial improvements in performance. The percentage increase is lower in recent years, but the overall performance of the birds has improved, particularly feed efficiency. It should be noted that the length of test period has changed from 20 to 13 days (see footnote b). If one corrects for normal day-old weights, the rate of gain is equal to or superior in the first 13 days in 1976 as it was for the first 20 days in 1964. The change is greater for the controls than for the penicillin treated, another indication that the reduction in percentage improvement due to antibiotics is a result of improved performance of controls rather than a regression of the penicillin treated birds. Waibel et al. (556) titled a

paper "Disappearance of a Growth Response in Chick to Dietary Antibiotics in an Old Environment." Heth and Bird (223) summarized the data from the same laboratory used by Waibel et al. but over a longer period of time and found the average responses to be similar for 1950-53 as compared with 1956-59 (Table 21).

TABLE 21

GROWTH RESPONSE OF CHICKS TO ANTIBIOTICS FROM 1950 to 1961[a]

Antibiotic Period	No. Trials	Average Response % of Controls
Tetracycline, 10-35 ppm		
1950-1953	31	112.3
1955-1960	29	110.2
Penicillin, 4-30 ppm		
1950-1953	46	108.5
1956-1959	15	110.2
Zinc Bacitracin, 10-35 ppm		
1956-1959	16	105.9
Zinc Bacitracin, 100 ppm		
1956-1959		115.2

[a]Heth and Bird, 223.

Heth and Bird (223) and Libby and Schaible (296) reported that in a given environment the growth response of chicks to an antibiotic may be reduced but noted that the general level of growth increased during the time period, leading the authors to conclude that antibiotics had reduced the number of harmful organisms in the environment so that the control chicks grew better, rather than the antibiotic fed birds regressing to the control level.

The improved performance of controls with time should not all be attributed to a reduction of suppressive organisms; genetic and dietary progress has also been made. The improvement in diets should also result in a decrease in percentage response to antibiotics as discussed in the section on mode of action. Other than the instance cited above of using penicillin as a control drug in screening tests (Table 20), the continuous use of a single antibiotic has not been critically evaluated, as it is not general practice for a live-

stock producer or a researcher to feed antibiotics throughout the animal's life cycle or to use the same antibiotic year after year. However, numerous experiments have been carried out that shed some light on whether the more commonly used antibiotics are continuing to improve the performance of animals. Elliot and Johnson (157b) conducted several experiments on a single commercial swine farm over a period of six years. A summary of their evaluation of a combination of chlortetracycline, penicillin and sulfamethazine is presented in Table 22.

TABLE 22

EFFECT OF FEEDING ANTIBIOTICS ON WEIGHT GAINS OF SWINE, IN TESTS ON A SINGLE COMMERCIAL FARM, 1960-1965[a,b]

Date Experiment Started	Average Daily Gain			Feed Efficiency[c]		
	Controls (g)	+ Antibiotic (g)	Improvement (%)	Controls	+ Antibiotic	Improvement (%)
Dec. 1960	263	413	57	2.13	2.11	1.0
Mar. 1961	222	395	78	2.08	1.85	11.1
Apr. 1962	186	359	93	2.15	1.81	15.8
May 1964	191	336	76	2.99	2.18	27.1
Sept. 1964	200	322	61	2.71	2.36	12.9
Oct. 1965	250	331	32	2.77	2.28	17.7

[a] Elliott and Johnson (157b).

[b] Antibiotic: 100 g. of chlortetracycline, 100 g. of sulfamethazine and 50 g. of penicillin per ton of diet for pigs 3 to 9 weeks of age.

[c] Units of feed per unit of gain.

This swine producer had routinely fed diets containing chlortetracycline, but not penicillin and sulfamethazine, during the entire period. Other antibiotics may have been fed intermittently for short periods. The average performance and the response within any one year varied probably as a result of the environmental conditions, including stresses, existing at the time the experiment was conducted. But, after six years of testing, the combination of chlortetracycline, sulfamethazine and penicillin resulted in a 32% improvement in rate of gain and an 18% improvement in feed efficiency.

Hays (211b) conducted an experiment on the same commercial swine farm that Elliot and Johnson used. The results of that experiment are presented in Table 23.

TABLE 23

EFFECT OF FEEDING ANTIBIOTICS AT HIGH LEVELS ON WEIGHT GAINS OF YOUNG PIGS[a, b]

Antibiotic	Level of Feeding (g/ton)	Daily Gain		Feed/Gain[c]	
		Average (g)	Improvement (%)	Average	Improvement (%)
Control	0	318		2.30	
Penicillin-streptomycin[d]	250	454	43	1.98	13.9
Chlortetracycline-sulfamethazine-penicillin	250	427	34	1.94	15.7
Penicillin-streptomycin[d]	100	395	24	2.02	12.2
Chlortetracycline	100	396	25	2.14	7.0

[a]V. W. Hays (unpublished data, experiment 6443, Iowa Agr. Home Econ. Exp. Sta., 211b).

[b]Average initial weight of pigs, 8.67 kg.; 4 pens of 10 pigs each per treatment, 34 days on test. Pigs nursed sows prior to going on experiment.

[c]Unit of feed per unit of gain.

[d]1:3 ratio of procaine penicillin to streptomycin.

[e]100 g. of chlortetracycline, 100 g. of sulfamethazine and 50 g. of penicillin per ton of diet.

The response to the antibiotic combination was similar for the two studies: an improvement of 32% and 34% in growth rate and an improvement of 16% and 18% in feed conversion for the two tests conducted in 1965 (Tables 22 and 23). Table 23 also shows a 7% improvement in feed conversion and a 25% improvement in rate of gain resulting from the addition of chlortetracycline, though it had been used extensively on the farm for at least five years. The combination of penicillin and streptomycin resulted in similar improvements in performance.

The results of similar tests using tylosin from 1959 to 1966 are summarized in Table 24 (Jordan, 262b).

TABLE 24

EFFECT OF FEEDING TYLOSIN FOR A PROLONGED PERIOD ON WEIGHT GAINS OF PIGS[a]

Years	Experiments	Average Daily Gain			Feed/Gain		
		Controls (g)	Plus Tylosin[b] (g)	Improvement (%)	Controls	Plus Tylosin[b]	Improvement (%)
1959-1960	3	445	490	10	1.98	1.92	3.0
1961-1962	1	454	499	10	2.21	2.12	4.1
1963-1964	1	254	286	13	1.90	1.80	5.3
1965-1966	3	277	327	18	2.20	2.04	7.3
1959-1960	1	409	490	20	2.33	2.15	7.7
1965-1966	1	281	304	8	2.32	2.05	11.6

[a]Jordan (262b).

[b]100 g. of tylosin per ton of diet, except for last 2 lines in which the level of tylosin was 40 g/ton.

The rates of gain and feed conversion by the animals in the later experiments were less than in the earlier years, which Jordan attributes to change in the management program and use of a more simplified diet which contained little or no milk products. The percentage of response is actually greater in 1965-1966 as compared with 1959-1962, in keeping with the previous examples of an increased response for animals under nutritional stress.

Hays and Baker (212b) conducted an experiment specifically to test the response to chlortetracycline in a confinement swine unit in which the antibiotic had been continuously used for more than three years. The unit housed 650 to 700 pigs continuously for the three-year period, which would allow ample time for resistance problems to develop. Though the resistance patterns of the intestinal organisms were not determined we can state with confidence, from our present knowledge of antibiotic resistance, that the intestinal coliforms were solidly resistant to tetracyclines and that resistance was a multiple and transferable type. As illustrated in Table 25, chlortetracycline (50 g/ton) resulted in a 10.2% improvement in growth rate and a 1.0% improvement in feed efficiency.

TABLE 25

EFFECTS OF CHLORTETRACYCLINE ON WEIGHT GAINS OF PIGS AFTER CONTINUED USE[a, b]

Group	Average Daily Gain (g)	Improvement (%)	Feed Efficiency[c]	Improvement (%)
Control (36 pigs)	577		2.97	
Fed chlortetracycline[d] (35 pigs)	636	10.2	2.94	1.0

[a] Hays and Baker (212b).

[b] Chlortetracycline had been used continuously in the building for 3 years before the test, and pigs had received chlortetracycline before the start of the experiment.

[c] Units of feed per unit of gain.

[d] 50 g. of chlortetracycline per ton of diet.

A thorough evaluation of available data suggests that those antibiotics found to be effective as feed additives in the 1950's are still effective in the 1970's. The magnitude of the response varies from experiment to experiment; caution must be used in basing conclusions on one experiment. Such a cautionary statement should not be necessary for a researcher in biology, but normal biological variation may not be well understood by those not experienced in conducting animal experiments and in the principles of biostatistics. Such variability may not be appreciated by those researchers who are experienced only in *in vitro* work in which greater control of the environment can be accomplished.

IV. Effectiveness of Antibacterial Agents in Swine Feeding Programs

Tables 5, 26 and 27 present a summarization of data from journal articles, field day reports and unpublished data secured through private communications from research workers.

TABLE 26

RESPONSE OF PIGS TO ANTIBIOTICS DURING THE GROWER-DEVELOPER STAGE (35 TO 125 POUNDS BODY WEIGHT)

Antibiotic	Number[a]			Wt., lb.[b]		ADG, lb.[c]			Feed/Gain[c]		
	Exp.	Rep.	Pigs	I	F	-	+	% Imp.	-	+	% Imp.
Tetracyclines[d]	120	325	1851	35	111	1.28	1.42	10.93	3.09	2.97	3.88
Bacitracin[e]	22	51	328	39	109	1.37	1.44	5.10	2.80	2.73	2.50
Tylosin[f]	27	71	968	39	110	1.28	1.42	10.94	2.86	2.74	4.20
Virginiamycin[g]	52	142	985	38	114	1.31	1.45	10.69	2.88	2.69	6.60
Bambermycins[h]	8	45	372	44	112	1.63	1.67	2.45	2.56	2.53	1.17
Chlortetracycline-sulfathiazole-penicillin[i]	3	4	33	44	159	1.35	1.58	17.03	2.91	2.82	3.09
Chlortetracycline-sulfamethazine-penicillin[i]	24	58	493	41	91	1.25	1.47	17.60	2.63	2.45	6.84
Tylosin-sulfamethazine[j]	5	13	156	45	110	1.56	1.64	5.12	2.79	2.73	2.15
Carbadox[k]	15	63	463	34	90	1.19	1.37	15.13	2.75	2.56	6.91
SUMS	276	772	5649								
WEIGHTED AVG.				37	109	1.31	1.45	10.68	2.91	2.78	4.47
Tetracyclines:											
1950-1956	51	146	802	36	104	1.21	1.42	17.36	3.19	2.99	6.27
1957-1966	51	122	686	35	115	1.33	1.41	6.02	3.07	3.01	1.95
1967-1977	18	57	363	35	121	1.34	1.42	5.97	2.89	2.82	2.42
Chlortetracycline-sulfamethazine-penicillin:											
1957-1966	9	24	167	39	82	1.15	1.41	22.61	2.75	2.54	7.64
1967-1977	18	38	359	42	108	1.32	1.52	15.15	2.62	2.46	6.11

[a] Number of experiments and number of replications (pens) and pigs per treatment.

[b] Initial and final weight, lb.

[c] Average daily gain and feed/gain for pigs fed diets without (-) or with (+) antibiotics.

[d] Chlortetracycline and oxytetracycline. References: 24, 26, 27, 28, 30, 34, 37, 38, 45, 50, 57, 72, 80, 82, 83, 97, 130, 147, 154, 191, 205, 219, 220a, 221, 222, 246, 255, 256, 294, 302, 306, 343, 347, 349, 350, 375, 398, 409, 423, 425, 427, 494, 497, 498, 525, 530, 540, 543, 547, 548, 553, 563, 579, 93, 102, 126a, 227.

[e] References: 34, 55, 72, 120, 130, 255, 256, 279, 347, 356, 408, 427, 494, 524, 579.

[f] References: 34, 35, 191, 220b, 265, 279, 280, 335, 343, 347, 375, 380, 398, 409, 427, 434, 553, 579.

[g] References: 26, 28, 34, 35, 153b, 191, 214, 262a, 285, 302, 343, 345, 347, 380, 425, 434.

[h] References: 335, 356, 547.

[i] Chlortetracycline, penicillin and sulfamethazine or sulfathiazole. References: 2, 4, 103, 220b, 278, 356, 357, 375, 380, 385, 408, 529b, 589, 344, 457.

[j] Tylosin-sulfamethazine. References: 344, 408.

[k] References: 4, 298, 375, 380, 381, 494, 529b, 213.

TABLE 27

RESPONSE OF PIGS TO ANTIBIOTICS DURING THE GROWING-FINISHING STAGE (TESTS CONTINUED TO MARKET WEIGHT)

	Number[a]			Wt., lb.[b]		ADG, lb.[c]			Feed/Gain		
	Exp.	Reps.	Pigs	I	F	–	+	% Imp.	–	+	% Imp.
Penicillin-streptomycin[d]	34	74	557	49	194	1.55	1.61	3.87	3.44	3.38	1.74
Bacitracin[e]	29	106	491	52	206	1.60	1.64	2.50	3.37	3.28	2.67
Tetracycline[f]	108	348	2325	40	199	1.52	1.62	6.58	3.53	3.44	2.55
Tylosin[g]	26	105	758	53	201	1.51	1.58	4.64	3.41	3.36	1.47
Bambermycins[h]	12	52	461	59	207	1.59	1.62	1.89	3.42	3.38	1.17
Virginiamycin[i]	21	86	514	43	206	1.57	1.66	5.73	3.38	3.27	3.25
Arsenicals[j]	42	158	490	32	134	1.35	1.36	0.74	2.96	2.94	0.68
Nitrofurans[k]	7	14	70	52	201	1.41	1.43	1.42	3.39	3.37	0.58
SUMS	279	943	5666								
WEIGHTED AVG.				44	190	1.51	1.57	3.97	3.37	3.30	2.08
Penicillin-Streptomycin:											
1950-1956	6	9	54	30	185	1.53	1.68	9.80	3.55	3.28	7.61
1957-1966	16	32	258	48	188	1.56	1.62	3.85	3.44	3.42	0.58
1967-1977	12	33	245	61	207	1.54	1.57	1.95	3.39	3.38	0.29
Tetracyclines:											
1950-1956	44	163	869	39	199	1.49	1.63	9.40	3.74	3.57	4.55
1957-1966	34	78	764	37	195	1.53	1.62	5.88	3.50	3.46	1.14
1967-1977	30	107	692	44	204	1.54	1.61	4.55	3.25	3.22	0.92
Bacitracin:											
1950-1956	5	6	40	37	199	1.49	1.50	0.67	3.70	3.60	2.70
1957-1966	1	2	12	40	184	1.56	1.54	-1.28	3.55	3.26	8.17
1967-1977	23	98	439	56	208	1.63	1.68	3.06	3.29	3.21	2.44

[a] Number of experiments and number of replications (pens) and pigs per treatment.

[b] Initial (I) and final (F) weights, lb.

[c] Average daily gain and feed/gain for pigs fed diets without (–) or with (+) antibiotics.

[d] Combination of penicillin and streptomycin. References: 55, 137, 147, 180, 221, 254, 256, 265, 280, 398, 408, 543, 553.

[e] References: 69, 117, 120, 129, 256, 279, 356, 385, 398, 408, 494, 524, 589.

[f] Chlortetracycline and oxytetracycline. References: 21, 26, 28, 31, 39, 51, 55, 71, 72, 80, 83, 98, 100, 129, 173, 187, 191, 196, 202, 205, 215, 220a, 221, 222, 239, 246, 255, 291, 294, 302, 343, 375, 398, 402, 409, 437, 494, 541, 542, 543, 547, 548, 553, 564, 565, 579, 590, 594, 70, 75, 77, 121.

[g] References: 129, 221, 265, 280, 291, 335, 343, 375, 398, 408, 409, 529b, 553, 579, 589.

[h] References: 335, 341, 356, 375, 408, 494, 547.

[i] References: 26, 28, 129, 191, 214, 285, 302, 343.

[j] Includes arsanilic acid and 3-nitro-4-hydroxy phenylarsanic acid and experiments for all stages of production. References: 24, 37, 69, 78, 108a, 127, 204, 210, 294, 375, 398, 425, 494, 175.

[k] References: 25, 391.

Efforts were made to omit data from studies in which nutrient deficiencies were involved. For example, some of the earlier studies with antibiotics were designed to evaluate the feed grade sources of antibiotics as contributors of both the antibiotic and "animal protein factor" or vitamin B_{12}. Studies that involved feed ingredients such as raw soybeans, which exaggerate the antibiotic response, were also excluded. Those studies in which the animals were fed individually in metabolism cages were excluded as these represent an abnormal situation in which little or no response to the antibiotic can or should be expected. In addition, the data are primarily limited to experiments conducted in the United States. Since management and housing practices as well as diets and feeding management differ from country to country and these affect the response to antibiotics, it is deemed advisable to emphasize U.S. data.

The average responses to the individual antibacterial agents or commonly used combinations are presented in the upper part of the tables; for some, the results are reported by year periods (1950-56, 1957-66 and 1967-77) in the bottom part of the tables. The three tables cover the three stages of production for which it is a common practice to make ration changes: starter (Table 5), grower (Table 26) and finisher (Table 27).

All researchers do not follow the same procedures; it has been necessary to make some arbitrary decisions as to which experiments to include in each summary. Table 5 includes those experiments in which pigs weighed less than 35 pounds initially and were continued on the diets to a maximum weight of 75 to 80 pounds. The summary for the grower phase (Table 26) includes those experiments in which pigs weighed more than 35 pounds and were continued on experiment until they weighed 125 to 150 pounds. The growing-finishing summary includes data to market weight (Table 27).

As is commonly observed, the responses are much greater during the starter phase and decline as the pig matures. This is particularly noticeable if the differences are expressed as a percentage of the controls. For example, the differences between controls and pigs supplemented with antibiotics in mean daily gain for all experiments is 0.14 pounds per day for both the starter and the grower phase (Table 5 and 25). However, when expressed as a percentage of the mean daily gain by control pigs, the 0.14 represents 16.09% improvement during starter phase and 10.69% improvement during the grower phase.

It is obvious from the results presented in the tables that all antibiotics are not equally effective for swine. Even though a drug may be approved by the Food and Drug Administration as an additive to improve rate and efficiency of gain, there is no required assurance that it be equally effective or superior to the previously approved antibacterials. Similar differences in responses were reported in 1953 by Braude et al. (Table 28) and in 1954 by Lasley et al. (Tables 29 and 30).

TABLE 28

GROWTH AND FEED EFFICIENCY IN DIETS OF GROWING-FINISHING PIGS FED DIETS FORTIFIED WITH VARIOUS ANTIBIOTICS [a]

Antibiotic	No. Comparisons		Improvement in Performance, %	
	ADG	F/G	ADG	F/G
Chlortetracycline	187	146	36	9.8
Oxytetracycline	23	17	24	6.1
Penicillin	53	44	11	5.7
Streptomycin	50	41	15	5.6
Bacitracin	12	10	9	-7.0
Chlormycetin	6	3	6	1.7
Neomycin	4	4	-7	12.4

[a]Adapted from Braude et al, 67.

TABLE 29

RESPONSE BY WEANLING PIGS FED ANTIBIOTICS IN DRY LOT[a, b]

Number of Experiments	Antibiotic	Improvement in Performance, %	
		ADG	F/G
24	Chlortetracycline	18	3.5
8	Oxytetracycline	17	2.5
5	Penicillin	18	5.3
9	Streptomycin	17	5.5
2	Bacitracin	2	2.6
48	Average	17	3.9

[a]Includes experiments in which pigs were fed to near 200 pounds body weight.

[b]Adapted from Lasley et al. (289).

TABLE 30

EFFECTS OF ANTIBIOTICS ON PERFORMANCE AND SURVIVAL OF GROWING-FINISHING PIGS[a]

Weight, lb.				Controls			+ Antibiotic		
Initial	Final	Antibiotic	Pigs Started[b]	No. Pigs	ADG	F/G	No. Pigs	ADG	F/G
43	171	Penicillin	20	20	1.38	3.95	19	1.38	3.70
68	208	Streptomycin	40	38	1.68	3.92	40	1.77	3.64
64	193	Chlormycetin	30	27	1.45	3.81	30	1.55	3.67
52	155	Chlortetracycline	16	13	.98	5.34	15	1.21	4.34
35	174	Penicillin	14	13	1.10	3.98	14	1.32	3.58
35	176	Chlortetracycline	14	13	1.10	3.98	13	1.30	3.63
44	180	Penicillin	20	20	1.48	3.95	20	1.46	3.63
60	192	Penicillin	50	47	1.49	3.80	49	1.64	3.67
43	175	Chlortetracycline	20	20	1.37	3.95	20	1.45	3.61
44	182	Chlortetracycline	20	20	1.47	3.95	20	1.52	3.70
50	187	Chlortetracycline	30	29	1.40	3.76	29	1.78	3.41
	Total Pigs		274	260			269		
	% Survival			94.9			98.2		
	Avg. daily gain & avg. feed/gain				1.35	4.03		1.49	3.69
	% Improvement						3.5	10.4	8.4

[a]Adapted from Lasley et al. (289).

[b]Per treatment.

It is obvious from these summaries that antibacterial agents are not equally effective in improving growth rate and feed efficiency. In general, those of a broader antibacterial spectrum (singly or in combinations) are more effective.

Copper sulfate is used extensively in Great Britain as a feed additive and has been tested thoroughly in this country. When copper sulfate is added at a dietary level of 250 ppm of elemental copper, an additive effect of antibiotics is usually not observed, indicating a similar mode of action for the copper and antibiotics. Petitions to our regulatory agencies for similar use in this country have not been approved, with certain concerns being expressed about increased copper levels in tissues and adding excess copper to the environment. These are complicated and debatable issues and beyond the scope of this paper. The experimental work on effects of copper on growth rate and feed conversion has been thoroughly reviewed by Braude (63) and is summarized in Tables 31 and 32. As with antibiotics, there are variations among reports on the actual magnitude of rate of gain and feed/gain responses. In Braude's review, the average improvement in rate of gain was 8.7% and for feed conversion, 6.6% when copper (250 ppm) was added to the diet. Lower levels of copper resulted in responses of a lower magnitude (Table 31).

TABLE 31

RESPONSE OF PIGS TO VARYING LEVELS (PPM) OF DIETARY COPPER[a]

Level of Cu, ppm	Number of Experiments	Improvement in Performance, %	
		Average Daily Gain	Feed/Gain
125	38	4.4	3.4
150-180	10	3.6	3.1
200	7	4.4	3.9
250	202	8.7	6.6

[a]Adapted from Braude (63).

The average responses for 1955-1965 and 1965-1975 were quite similar (Table 32).

TABLE 32

EFFECTS OF COPPER (250 PPM) ON PERFORMANCE OF PIGS[a]

Time Period	No. Experiments	Total Pigs Per Treatment	Improvement in Performance, %	
			Average Daily Gain	Feed/Gain
1955-65	83	1215	8.1	5.4
1965-75	119	2630	9.1	7.4

[a]Adapted from Braude (63).

It is obvious that some of the gains in production efficiency attributed to antibiotics could be achieved by the use of other antimicrobial agents such as copper compounds, arsenicals, nitrofurans and carbadox; however, the trade-offs in absolute efficacy or safety have not been thoroughly researched or discussed. Restricting the use of one or a few agents will naturally result in greater use of those not similarly restricted. The use of other agents, which have not been thoroughly evaluated over an extended period, may be more detrimental than the concerns presently being expressed about tetracyclines and penicillin.

There is ample evidence that species, age of animal or stage of production, adequacy of diet and environmental conditions are all important factors affecting the response to antibiotics. Each of these factors must be considered when selecting an antibiotic to use, level to feed and duration of feeding. The examples in the sections on "Mode of Action" and "Continued Effectiveness" will serve to illustrate effective application in feeding programs. Only a few additional comments and illustrations of particular benefits regarding swine will be presented.

The use of a high level of antibiotics in the diet of sows at breeding time increases conception rate and litter size. Table 33 summarizes a number of studies that involved more than 1300 sows and show an average 7% improvement in conception rate at first estrus and 0.4 more live pigs farrowed per litter.

TABLE 33

THE EFFECT OF ANTIBIOTICS AT BREEDING TIME ON FARROWING RATE AND LITTER SIZE

No.	Farrowing Rate, %		Live Pigs/Litter		
Sows	Control	Treated	Control	Treated	Reference
377	68.5	82.9[a]	9.8	10.1[a]	Messersmith <u>et</u> <u>al</u>., 342
59	-	-	7.1	9.7[b]	Dean and Tribble, 144
96	87.5	95.8[c]	9.0	10.3[c]	Ruiz <u>et</u> <u>al</u>., 433a
182	60.9	70.0[c]	9.8	10.0[c]	Krug, 287
249	66.9	75.4[a]	9.9	10.2[a]	Myers and Speer, 372
192	93.8	91.6[d]	10.9	11.3[d]	Mayrose <u>et</u> <u>al</u>., 323
239	70.8	72.3	10.2	10.4	Soma & Speer, 491, 490
Weighted Avg.	72.6	80.0	9.9	10.3	

[a]Chlortetracycline, 0.5 to 1.0 g/sow/day.

[b]Chlortetracycline, 0.5 to 1.0 g/sow/day, 0.54 g/sow/day.

[c]Chlortetracycline, sulfamethazine and penicillin at 0.5, 0.5 and 0.25 g/sow/day, respectively.

[d]Tylosin phosphate, 0.6 g/sow/day.

Speer (493) summarizes additional unpublished data on both tetracycline and tylosin which in some cases show an even larger difference in conception rate than shown in Table 33. A high level of an absorbable antibiotic seems necessary to elicit this response. This is reasonable since conception rate or litter size problems are likely associated with systemic rather than gastrointestinal problems. Using embryo survival to 28 days as an indicator of reproductive performance, Sosa et al. (492) reported that tylosin improved the number of live embryos but that bacitracin did not. Neither of these antibiotics are particularly well absorbed, but tylosin appears to be more effective against systemic infections.

Young growing pigs show a markedly greater and more consistent response to antibiotics than do more mature animals. Table 34 provides a typical illustration of the greater response of very young pigs as compared with that of older pigs.

TABLE 34

EFFECT OF FEEDING OLEANDOMYCIN AT DIFFERENT LEVELS ON PERFORMANCE OF PIGS[a]

Pigs Tested and Level of Oleandomycin Fed	Average Wt. (kg)		Daily Gain		Feed Efficiency[b]	
	Initial	Final	Average (%)	Improvement (%)	Average	Improvement (%)
Baby pigs[c]						
No oleandomycin	4.29	8.91	163		2.02	
2.5 g/ton	4.18	10.13	213	30.7	1.73	14.4
5 g/ton	4.10	10.07	213	30.7	1.62	19.8
10 g/ton	4.34	10.70	227	39.3	1.69	16.3
20 g/ton	4.35	10.98	236	44.8	1.62	19.8
Growing pigs[d]						
No oleandomycin	13.26	34.41	527		2.82	
5 g/ton	13.35	36.18	572	8.5	2.60	7.8
10 g/ton	13.21	35.96	563	6.8	2.52	10.6
20 g/ton	13.44	35.87	563	6.8	2.63	6.7

[a] Hawbaker et al. (209).

[b] Units of feed per unit of gain.

[c] Initial age 13 days.

[d] Initial age 51 days.

Oleandomycin was fed to the two groups of pigs. In baby pigs, the antibiotic resulted in an increase in growth rate of 30% to 44% and an improvement in feed efficiency of 14% to 20%. In the older pigs, the antibiotic resulted in an improvement of 7% to 10% in growth rate and efficiency. This age effect is further illustrated by the data in Tables 5, 26 and 27.

The diets used today to evaluate the effectiveness of antibiotics are, in general, more adequately balanced to meet the animals' needs than were the diets used in the early 1950's. There are two main reasons for this: more information is available regarding the nutrient needs; some nutrients, particularly the vitamins, are less expensive today. The feeding of nutritionally balanced diets reduces but does not eliminate the response to antibiotics. Certain developments may have offset some of the gains made possible by greater knowledge about nutrient requirements. For example, the performance of pigs during the starter phase in 1957 to 1966 is not as good as in 1950-1956 (see bottom of Table 5). During the early 1950's most early weaned pigs were started on diets high in milk products. The cost of milk products has resulted in a reduction in the use of this highly digestible source of protein and carbohydrate. The diet changes probably explain the greater response in antibiotics in 1957-1966 as compared with 1950-1956. Another illustration in the tables which should be noted is the improvement in feed/gain ratios with time for the growing-finishing pigs. If the data is averaged for penicillin-streptomycin, tetracyclines and bacitracin, there has been a 9.6% change in feed conversion of control animals as compared with a 6.0% for the antibiotic treated animals. Assuming that the genetic potential is the same for the antibiotic treated and control groups, the data support the earlier cited observations of Waibel et al. (556) and Libby and Schaible (296) that a portion of the reduction in percentage responses is a result of improvement of the controls rather than a decline in the effectiveness of the antibiotic.

A statistical evaluation of the tetracycline data (120 experiments) in Table 26 revealed no significant year by treatment interaction for feed/gain ratios. There was a significant linear improvement in feed conversion with time (0.011 lb/yr) with a constant predicted improvement ($P<01$) of 0.10 lb. of feed per pound of gain for the treated group as compared with controls. There was evidence of a treatment by year interaction for rate of gain. Regression analysis showed no significant change with time for the treated group, but a significant increase in growth rate of controls to 1962 and a constant rate thereafter. The initial difference in 1950 was about 0.2 lb. per day; this difference declined to approximately 0.08 lb/day by 1962 and remained constant thereafter. This improvement in performance of controls relative to no change in performance of treated animals is consistent with the previously cited observations of Waibel et al. (556) and Libby and Schaible (296) for poultry. The observation was probably first expressed, but not published to my knowledge, by the late Damon V. Catron.

The improvement in feed/gain ratios accompanied by little, if any, change in rate of gain with time reflects the selection emphasis in the swine industry. More selection pressure has been put on reducing fatness in pigs. This leads indirectly to a reduction in total feed required per unit of live weight gain. This has probably had an even greater impact on reducing feed required per unit of gain than any direct efforts to select for improved efficiency.

Hygienic conditions in swine production have not greatly improved in recent years. Though greater knowledge about the role of hygiene in animal performance has been gained and producers are expending greater effort in this regard, other changes in systems of production have occurred that partially offset the advances made in sanitation practices. These changes have been necessitated by the increased value of land and a marked reduction in available labor. Producers are finding it necessary to specialize in fewer livestock enterprises and to confine their animals to smaller spaces in order to release land for alternative uses and to facilitate the mechanization of feeding and disposing of wastes.

Such intensification of production accentuates some of the environmental factors affecting responses to antibiotics. The increased concentration of animals in limited space can lead to a higher incidence of clinical and subclinical disease because of the greater ease of transmittal. Fortunately, the use of antibiotics has contributed to the success of many of these intensive units. Feed additive usage results in the greatest responses during periods of natural or imposed stresses. In pigs the greatest responses are observed at breeding or farrowing in sows, at weaning in young pigs and during the stresses associated with relocation, such as movement of feeder pigs. Similar situations apply to other species.

V. Effectiveness of Antibacterial Agents in Feeding Programs for Growing Chicks and Layer Hens

The factors affecting the response of chickens to antibiotics are similar to those affecting the responses by pigs. The management programs are, however, very different. Because of the ability to provide nearly unlimited day-old chicks at a given time, much more rigorous control over the genetic background of the chicks, the management procedure of all-in, all-out systems of productions, different disease and parasite problems, and the many other differences in production procedures and problems, it is obvious that the need for and conditions for use differ markedly between poultry and swine.

The antibacterial agents which are useful for the two species are generally the same. It does appear that certain drugs, for example bacitracin and penicillin alone, are more effective in poultry than in swine. In swine feeding programs the application of bacitracin has been limited primarily to the growing-finishing stage, whereas in chicks it has been used extensively in the starter stage. Penicillin has been used very extensively in poultry feeding programs; it has usually been used in combination with other drugs (streptomycin, bacitracin, chlortetracycline, etc.) in swine feeding programs.

The examples cited illustrate the responses of growing chicks to antibacterial agents. These responses are summarized in more detail in Table 35 for chicks to about four weeks of age and in Table 36 for chicks to approximately eight weeks of age.

TABLE 35

SUMMARY OF CHICK PERFORMANCE TO ABOUT 4 WEEKS

Antibiotic	Chick Wt. n[a]	Chick Wt. -	Chick Wt. +	Chick Wt. % Imp.[b]	Feed/Gain n[a]	Feed/Gain -	Feed/Gain +	Feed/Gain % Imp.[b]
Tetracycline[d]	174	397.2[c]	426.3[c]	7.33	106	2.16[c]	2.05[c]	5.09
Penicillin[e]	155	334.1	361.2	8.11	77	2.02	1.93	4.46
Bacitracin[f]	73	418.6	445.0	6.30	34	1.85	1.79	3.24
Arsenicals[g]	61	354.6	372.1	4.94	16	2.14	1.99	7.01
Streptomycin[h]	17	472.5	506.8	7.26	11	2.64	2.59	1.89
Virginiamycin[i]	10	233.4	270.7	15.98	4	2.54	2.31	9.06
Nitrofurans[j]	8	408.5	395.1	-3.28	1	1.53	1.57	-2.61
Oleandomycin[k]	26	459.4	482.4	5.01	23	1.78	1.74	2.25
Lincomycin[l]	6	344.8	376.7	9.25	6	1.57	1.44	8.28
Bambermycins[m]	24	485.5	503.8	3.77	24	1.67	1.64	1.80
Erythromycin[n]	7	334.6	358.7	7.20	7	1.98	1.88	5.05
Tylosin[o]	4	277.0	284.8	2.82	4	2.00	1.98	1.00
Weighted avg.	565	382.0	407.7	6.72	313	2.03	1.94	4.43

[a] n = number of comparisons (experiments).

[b] Percentage improvement in performance due to antibiotics.

[c] Average weight (g) per bird and feed/gain for birds fed diets without (-) or with (+) antibiotics.

[d] Chlortetracycline and oxytetracycline. References: 40, 44, 48, 106, 132, 133, 140, 153a, 164, 178, 188, 192, 225, 227, 230, 282, 303, 307, 311, 314, 321, 361, 373, 393, 401, 432, 442, 450, 451, 452, 469, 489, 506, 507, 527, 539, 567, 569, 592, 593, 596.

[e] References: 1, 41, 60, 112, 132, 140, 164, 168, 170, 172, 188, 225, 227, 230, 233, 235, 261, 269, 295, 307, 314, 318, 319, 321, 352, 361, 367, 379, 414, 442, 462, 484, 506, 526, 527, 539, 567, 576, 596.

[f] References: 41, 106, 140, 168, 169, 171, 178, 188, 225, 307, 321, 318, 319, 320, 352, 361, 379, 392, 414, 527, 539, 567, 569, 596.

[g] References: 1, 87, 168, 169, 171, 295, 320, 367, 400, 450, 461, 556, 591.

[h] References: 140, 192, 225, 227, 261, 361.

[i] References: 163, 164, 379.

[j] References: 177, 368.

[k] References: 314, 361, 462, 586.

[l] References: 319, 320, 321, 352.

[m] References: 133, 319, 321, 352, 561.

[n] References: 361, 379, 527, 596.

[o] References: 361, 379, 527.

TABLE 36

SUMMARY OF CHICK PERFORMANCE TO ABOUT 8 WEEKS

	Chick Wt.				Feed/Gain			
Antibiotic	n[a]	-	+	% Imp.[b]	n[a]	-	+	% Imp.[b]
Tetracycline[d]	88	1192.1[c]	1236.1[c]	3.69	53	2.60[c]	2.54[c]	2.31
Penicillin[e]	54	1299.2	1337.3	2.93	38	2.54	2.47	2.76
Bacitracin[f]	39	1425.2	1438.7	0.95	33	2.27	2.22	2.20
Arsenicals[g]	59	1285.5	1329.7	3.44	50	2.54	2.46	3.15
Bambermycins[h]	32	1483.3	1517.9	2.35	32	2.06	2.02	1.94
Lincomycin[i]	4	1734.5	1812.2	4.48	4	2.12	2.05	3.30
Nitrofurans[j]	3	1414.3	1442.3	1.98	2	2.05	2.02	1.47
Oleandomycin[k]	7	1483.0	1549.4	4.48	7	2.25	2.21	1.78
Total Number	286				219			
Weighted Avg.		1313.0	1351.6	2.94		2.42	2.36	2.48

[a] Number of comparisons (experiments).

[b] Percentage improvement in performance due to antibiotic.

[c] Average weight (g) per bird and feed/gain for birds fed diets without (-) or with (+) antibiotics.

[d] Chlortetracycline and oxytetracycline. References: 106, 133, 141, 178, 339, 442, 450, 472, 489, 572, 573, 574, 583, 592, 596.

[e] References: 261, 295, 319, 339, 321, 414, 442, 462, 472, 572, 573, 574.

[f] References: 42, 106, 135, 141, 178, 251, 319, 320, 321, 339, 414, 572, 574, 585.

[g] References: 135, 141, 171, 274, 275, 295, 318, 320, 351, 354, 400, 421, 450, 572.

[h] References: 133, 274, 275, 319, 321, 561.

[i] References: 319, 320, 321.

[j] References: 368.

[k] References: 462.

As was the case for the comprehensive summaries of swine data, researchers do not use the same length of trials, same diets, etc. Those experiments involving diets which greatly exaggerate the responses were excluded from these summaries. Certain dietary ingredients such as rye, improperly toasted soybean meal, etc., greatly exaggerate responses to antibiotics. These diets may be particularly helpful in screening antibacterial agents for effectiveness or the antibacterial agents may be beneficial in using such ingredients. The inclusion of these experiments in the summary could give a somewhat distorted evaluation of the overall effectiveness.

In Table 35 the weighted average of 565 experiments, which involved thousands of chicks, shows an average of 6.72 percent improvement in weights. In 313 of those experiments, data were also presented for feed required per unit of gain; the average response was 4.43%. Similar summaries to approximately 8 weeks of age were 2.94% improvement in chick weights and 2.48% improvement in feed conversion (Table 36).

There are differences in final average weights for the control birds for the different antibiotics presented in the summary. A part of these differences in weights can be related to the time span over which the antibiotics were tested and a part can be attributed to the fact that the summaries involved both layer breeds and broiler breed chicks and for some antibiotics a higher proportion of the experiments in the summary involved broiler breeds. For example, the experiments with lincomycin are limited to 1974-1977, whereas the tests with tetracyclines and penicillin cover the entire period of usage, 1950 to 1977. During the past 27 years tremendous genetic improvements in rate of weight gain and efficiency of feed conversion have been made. In the early 1950's it took more than 10 weeks to produce a 3.5 pound broiler and required 3.0 pounds of feed or more per pound of gain. Now, it takes less than 8 weeks time and the feed conversion may be 2 pounds of feed per pound of gain or less.

The mean responses presented in Tables 35 and 36 illustrate the effectiveness of the drugs in improving bird weights and feed conversion.

Summaries of the percentage responses to antibiotics since 1970 in comparison with all years are presented in Tables 37 and 38.

TABLE 37

IMPROVEMENT IN CHICK PERFORMANCE - ALL YEARS VS. SINCE 1970 (TO APPROXIMATELY 4 WEEKS OF AGE)[a]

	Weight, g				Feed/Gain			
	All Years		Since 1970		All Years		Since 1970	
Antibiotic	No.	% Imp.	No.	% Imp.	No.	% Imp.	No.	% Imp.
Tetracycline	174	7.33	24	6.79	106	5.09	19	5.38
Penicillin	155	8.11	45	12.20	77	4.46	28	7.14
Bacitracin	73	6.31	40	7.34	34	3.24	17	2.75
Arsenicals	61	4.94	25	4.71	16	7.01	8	4.81

[a] Data from Table 35.

TABLE 38

IMPROVEMENT IN CHICK PERFORMANCE - ALL YEARS VS. SINCE 1970 (TO APPROXIMATELY 8 WEEKS OF AGE)[a]

	Weight, g				Feed/Gain			
	All Years		Since 1970		All Years		Since 1970	
Antibiotic	No.	% Imp.	No.	% Imp.	No.	% Imp.	No.	% Imp.
Tetracycline	88	3.69	17	1.65	53	2.31	14	2.04
Penicillin	54	2.93	11	1.99	38	2.76	11	2.93
Bacitracin	39	0.95	33	2.72	33	2.20	22	2.42
Arsenicals	59	3.44	18	1.54	50	3.15	18	1.41

[a]Data from Table 36.

There is some variation but, in general, these summaries illustrate continued effectiveness. There have been many changes, as discussed previously, in the industry during that time span, and these changes can affect the magnitude of the response. To approximately 4 weeks of age, the average response to penicillin (12.20 vs. 8.11%) and bacitracin (7.34 vs. 6.31%) is higher for the time period since 1970 than for the overall period. For tetracyclines (6.79 vs. 7.33%) and arsenicals (4.71 vs. 4.94%) the trend is in the opposite direction. For feed conversion, the average response to tetracycline (7.14 vs. 4.46%) is greater since 1970 than for the entire time span. The average feed/gain response to bacitracin (2.75 vs. 3.24%) and to arsenicals (4.81 vs. 7.01%) is in the opposite direction. If all the environmental and genetic variations that existed in these indirect time comparisons were subject to critical evaluation, the real change in magnitude of response could possibly be determined. These data illustrate, however, the continued effectiveness of all four antibacterial agents. Table 38 presents a similar summary for chicks to 8 weeks of age. These data are possibly more consistent with the expected change in response to antibacterial agents over time with chicks. The progress accomplished in controlling some of the major poultry diseases including coccidiosis, the improvements in diet formulations and the improvements made in housing and ventilation should all contribute to a lower response to the antibacterial agents; however, there is evidence of continued effectiveness. These summaries are generally consistent with the conclusions of Bird (46). He limited his summary to broiler breed chicks and to experiments which continued to market weight and concluded that data from 1951 to 1968 did not show any trend toward decreased effectiveness of the four antibiotics (chlortetracycline, oxytetracycline, penicillin and bacitracin) having the longest history of use.

There is less data available for layer and breeder hens. Table 39 presents a summary of these data.

TABLE 39

SUMMARY OF EGG PRODUCTION, FEED PER DOZEN EGGS AND HATCHABILITY

Antibiotic	Egg Production, %				Feed/doz. Eggs, lb.				Hatchability, %			
	n[a]	–	+	% Imp.	n	–	+	% Imp.	n	–	+	% Imp.
Tetracycline[b]	39	52.9	59.2	11.91	22	5.50	5.01	8.91	16	74.9	76.0	1.47
Arsenicals[c]	33	59.8	61.2	2.34	30	5.43	5.36	1.29	17	72.3	76.5	5.81
Penicillin[d]	27	54.3	57.3	5.52	19	5.75	5.46	5.04	13	75.6	78.6	3.97
Bacitracin[e]	12	63.2	63.8	0.95	5	4.38	4.28	2.28	2	74.6	79.8	6.97
Bambermycins[f]	5	47.8	52.0	8.79	5	7.50	6.62	11.73	1	84.2	86.3	2.49
Erythromycin[g]	37	66.4	67.3	1.36	13	4.42	4.36	1.36	7	84.6	84.9	0.35
Others and Combinations[h]	91	62.1	63.9	2.90	28	4.89	4.64	5.11	13	78.6	81.7	
Weighted avg.	244	59.9	62.3		122	5.30	5.05		69	76.2	78.8	
Avg. Improvement,%				4.01				4.72				3.41

[a]Number of comparisons of hens fed diets without (–) or with (+) antibiotics.

[b]Chlortetracycline and oxytetracycline. Referencs: 10, 41, 52, 62, 90, 133, 136, 162, 226, 228, 229, 231, 404, 438, 463, 471, 528.

[c]References: 10, 11, 18, 85, 136, 143, 226, 228, 295, 301, 410, 529a, 575.

[d]References: 41, 52, 76, 85, 91, 125a, 133, 143, 155, 156, 228, 301, 370, 404, 405, 463, 529a.

[e]References: 41, 86, 156, 226, 252.

[f]Reference: 133.

[g]References: 136, 193, 194, 226, 382, 383, 415.

[h]References: 10, 11, 85, 91, 125a, 136, 143, 193, 194, 226, 228, 243, 286, 336, 387, 389, 404, 441, 463, 529a.

No attempt was made to separate time comparisons, as the available data is for the most part limited to the early years of the introduction of antibacterial agents into the feeding program. Most of the data on tetracycline and penicillin is from the 1950's; for erythromycin, from the 1960's; and for bambermycin, from the 1970's. In this table, 91 experiments were included in a grouping of others plus combinations. This grouping included drugs or combinations that were never approved plus those for which there may have been minimum data, and is only included to add credence to the other observations that antibacterial agents are beneficial.

The weighted average responses to the antibacterials listed were 4.01, 4.72 and 3.41% for egg production, feed required per dozen eggs and percent hatchability, respectively. Many of the experiments were based on a full laying-year period for the egg production and feed conversion. For hatchability, the data were frequently limited to much shorter periods. These overall average responses included only those experiments (as was the case for the growing data) for which the diets were formulated to be nutritionally adequate and did not include dietary ingredients that would exaggerate the response. There is the consistent opinion among researchers, as expressed in the literature, that the magnitude of the response is markedly influenced by temperature, humidity and other environmental stresses. Extreme cold weather (Ryan et al., 438; Nivas et al., 382) or extreme hot weather (Heywang, 228, 229, 231), which cannot be completely avoided due to year-around production in all areas of the country, increases the response to antibiotics.

A summary of field experiments by Melliere (336) is presented in Table 40.

TABLE 40

EFFECT OF TYLOSIN ON EGG PRODUCTION[a]

Item	Treatment		Improvement
	Controls	Tylosin	%
No. trials	14	14	
Hens per treatment	96,618	101,374	
Eggs/hen	172.1	175.6	2.0
Feed/doz. eggs, kg.	2.89	2.79	3.5

[a]Summary of 14 field trials, Melliere (336).

The averages of 2.0% improvement in egg production and 3.5% improvement in efficiency of feed conversion are similar in magnitude to that of the later stages of broiler production.

VI. Effectiveness of Antibacterial Agents in Feeding Programs for Turkeys

Potter (412) summarized the response of turkeys to antibiotics to the year 1971. For the starter period (0 to 4 weeks of age) he reported an average of 19.3 and 18.2% improvement in gains and 7.3 and 7.6% improvement in feed conversions for penicillin and tetracycline, respectively. To 8 weeks of age the responses were 18.1 and 16.8% improvement in gains and 10.0 and 10.1% improvement in feed/gain for penicillin and tetracycline, respectively. Potter reported on a few experiments in which the turkeys were taken to market weight. For penicillin the average response was 5.2 and 8.6% for gain and feed/gain response, respectively. Comparable data for tetracycline were 3.2 and -1.2%.

Summary Tables 41, 42 and 43 present average responses to several antibiotics.

TABLE 41

RESPONSE OF TURKEYS TO ANTIBIOTICS
(TO APPROXIMATELY 4 WEEKS OF AGE)

Antibiotic	Weight, g				Feed Gain			
	n[a]		+	Imp. %	n[a]		+	Imp. %
Tetracycline[b]	64	470	540	14.89	28	2.03	1.86	8.37
Penicillin[c]	53	503	580	15.31	18	1.78	1.64	7.87
Bacitracin[d]	32	489	537	9.92	23	1.70	1.62	4.71
Streptomycin[e]	17	516	558	8.14	7	1.92	1.83	4.69
Number	166				76			
Weighted avg.		489	554			1.86	1.73	
Improvement, %				13.29				6.98

[a]Number of experiments in which turkeys were fed diets without (−) or with (+) antibiotics.

[b]References: 5, 61, 116, 140, 303, 328, 329, 330, 361, 394, 399, 442.

[c]References: 61, 116, 140, 283, 308, 328, 329, 330, 361, 394, 442, 443, 454, 468, 476, 477, 479, 481, 500, 558, 570, 598.

[d]References: 105, 116, 206, 361, 363, 419, 442, 454, 516, 559, 568.

[e]References: 61, 140, 283, 328, 330, 361, 394, 559.

TABLE 42

RESPONSE OF TURKEYS TO ANTIBIOTICS
(TO APPROXIMATELY 8 WEEKS OF AGE)

Antibiotic	Weight, g n[a]	–	+	Imp. %	Feed/Gain n[a]	–	+	Imp. %
Tetracycline[b]	31	1453	1645	13.21	27	2.38	2.24	5.88
Penicillin[c]	24	1270	1400	10.24	12	2.49	2.35	5.62
Bacitracin[d]	55	2031	2132	4.97	45	1.83	1.78	2.73
Bambermycins[e]	16	3755	3931	4.53	16	1.97	1.92	1.92
Number	126				100			
Weighted avg.		1963	2101			2.08	2.00	
Improvement, %				7.03				3.85

[a]Number of experiments in which turkeys were fed without (–) or with (+) antibiotics.

[b]Chlortetracycline and oxytetracycline. References: 6, 12, 13, 61, 399, 453, 482, 483, 515, 554, 588.

[c]References: 13, 61, 266, 309, 442, 444, 473, 482, 515, 589.

[d]References: 19, 413, 417, 419, 420, 515, 516, 555, 562, 586.

[e]16 weeks of age rather than 8. Reference: 355.

TABLE 43

RESPONSE OF TURKEYS TO ANTIBIOTICS
(TO MARKET WEIGHT)

Antibiotic	Weight, lb. n[a]	–	+	Imp. %	Feed/Gain n[a]	–	+	Imp. %
Penicillin[b]	5	17.80	17.82	5.73	2	4.54	4.42	2.64
Bacitracin[c]	80	19.93	21.37	7.23	75	3.14	3.09	1.59
Number	85				77			
Weighted avg.		19.80	21.22			3.18	3.12	
Improvement, %				7.17				1.89

[a]Number of experiments in which turkeys were fed diets without (–) or with (+) antibiotics.

[b]References: 309, 444, 473, 476, 481.

[c]References: 19, 252, 310, 413, 418, 419, 513, 555.

The average responses are similar to those reported by Potter. The average weight responses were 13.3, 7.0 and 7.2% for data to 4 weeks, 8 weeks and market weight (20 to 24 weeks), respectively. Feed gain responses were 7.0, 3.8 and 1.9 for the same periods.

Responses of egg production, feed/egg and hatchability are presented in Table 44.

TABLE 44

EFFECTS OF ANTIBIOTICS ON RATE AND EFFICIENCY OF EGG PRODUCTION AND HATCHABILITY IN TURKEYS[a]

Item	Number Experiments	Antibiotic[b] -	Antibiotic[b] +	Improvement
Egg production, %	15	44.2	44.8	1.36
Feed/egg, g	9	516	483	6.40
Hatchability, %	16	70.0	70.0	—

[a]References: 14, 16, 19, 88, 142, 474, 557.

[b]Turkey hens fed diets without (–) or with (+) antibiotics.

Egg production was improved by 1.36% and feed/egg improved by 6.40%. Data available from 16 experiments indicate that antibiotics have little or no effect on hatchability. This differs from the results with chickens in which hatchability was improved an average of 3.4%.

VII. Effects of Antibiotics On Mortality and Morbidity

There is much less published data available on mortality and morbidity than for rate and efficiency of gain. Most of the swine reports do not include such data, probably because of the relatively small number of animals per experiment. Maddock (312) summarized a series of field experiments involving the antibacterial combination of chlortetracycline, sulfamethazine and penicillin and reported that 3.17% of the control pigs died as compared with 2.21% of the treated pigs. Those figures are based on 49 separate experiments involving 2,204 pigs. Table 30 includes mortality data for several antibiotic comparisons. The average mortality for the control groups was 5.1% as compared with 1.8% for the antibiotic treated group, based on 274 pigs per group. For the experiments presented in Table 10, the experimental records show mortality figures of 8.5% for the control groups and 3.8% for the treated groups. These experiments involved a total of 616 pigs.

White-Stevens and Zeibel (583) reported the mortality and condemnation rates for a large group of broilers (5,000 per treatment) on a farm where chronic respiratory disease was a recognized problem. Including chlortetracycline (100 g/ton) in the diet reduced mortality (2.8 vs. 10.7%), reduced culling or condemnation (0.1 vs. 1.3%), increased weight of birds (3.08 vs. 2.87 lb.) and markedly increased the total marketed weights (14,933 vs. 12,400 lb.).

A number of papers (62, 297, 263, 318, 351, 359, 365, 387, 404, 405, 410, 415, 438, 440, 463) include data on mortality; the general trend is toward a reduction in mortality from having antibiotic in the feed. In most experimental situations, mortality is relatively low and the researchers are usually not in a position to attribute mortality or survival to a specific dietary treatment and do not anticipate that their experiments will be included in a large summary in an attempt to assess average mortality.

VIII. Summary

Antibiotic feed supplements have now been used routinely and successfully in livestock and poultry production for more than 27 years. As the worldwide demand for animal protein increases, the use of antibacterial agents will become increasingly important for maintaining an efficient and competitive livestock industry. There can be no doubt that antibiotics continue to provide substantial economic benefits to both the producer and consumer of meat, milk and eggs.

The number of alternative antibiotics which have been proven effective in improving performance is relatively small. These antibiotics are those often found to be most effective in treatment of diseases. This observation is consistent with the evidence which supports the thesis that antibiotics result in improved performance through their control or prevention of specific or nonspecific diseases. These observations are significant since one is not likely to find antibiotics that are both particularly useful in improving performance of animals and that have no application in treatment of diseases. Additives other than antibacterials may result in improved rate and efficiency of gain. However, since their mode of action will likely be different, these additives will not replace or substitute for antibacterial agents.

The magnitude of the response to antibacterial agents varies with stage of life cycle, stage of production and the environmental conditions to which the animals are exposed. The response is greater in young animals than in more mature animals. The response is greater during critical stages of production such as weaning, breeding, farrowing, or immediately post hatching in chicks and turkeys. Environmental stresses such as inadequate nutrition, crowding, moving and mixing of animals, poor sanitation and high or low temperatures also contribute to increased responses. Such stresses are ordinary and to a large degree unavoidable.

A critical review of the average responses to the various antibacterial agents clearly indicates that there are marked differences in the magnitude and consistency of responses. In general, those with a broader spectrum of antibacterial activity and those that are effective against gram-negative bacteria result in the greatest and most consistent responses.

Comparisons of the responses to antibacterial agents in recent years with responses in the early period of use demonstrate that those extensively used are still of benefit in improving growth rate and efficiency. There is some evidence that the magnitude of the response has declined for some uses. In view of the progress in nutrition, housing, management, sanitation and other factors that affect the response to antibiotics, it is surprising that the decline is not greater. There is also evidence that consistent use of antibiotics results in actual improvement in performance of the control animals rather than regression of treated groups.

IX. Research Needs

The development of antibiotic resistance with loss in efficacy and possible compromise of therapy in humans and animals has been a primary concern since the introduction of antibiotics. It has been proposed that meat, milk and eggs from animals fed antibiotics contribute to the transferable drug resistance in the consumer. This assumption could be tested with proper interspecies experimentation. Careful epidemiological studies are needed to determine the source of antibiotic resistance in humans and to what degree that resistance originates in animals and their flora. Interspecies studies excluding humans could provide more satisfactory evidence than is available now, but animal-to-human and human-to-human transfer studies are needed.

There is evidence that resistance development and resistance transfer may be reduced or prevented by concurrent use of other drugs. The safety and efficacy of these should be fully studied. Use of such drugs could lead to continued application of present drugs and could also extend or increase their therapeutic efficacy.

Further research is needed to determine if chronic oral exposure of humans to antibiotics and low-level, feed-additive usage in animals compromises therapy in humans or animals. Even after extensive use of the tetracyclines and penicillin, they continue to be the primary drugs of choice for prophylactic and therapeutic use. A restriction in prophylactic or feed additive usage would likely increase therapeutic use, leading to total use at or above the present level. There is a need to determine whether therapeutic use or low level is the major contributor to resistance levels.

The modes of action for antimicrobial agents are still an area of major disagreement. It is recognized that animals are exposed to a very complex and ever-changing microflora; thus the specific modes of action may be complex and ever-changing. Little research effort has been devoted to the determination of the modes of action. This research could lead to alternative drugs or methods.

A thorough evaluation of the relative efficacy of currently available and new drugs is needed. Data on the older drugs permit indirect comparisons of the relative effects on performance, mortality and morbidity; much less data are available for direct comparisons. Greater emphasis on field evaluation of antibiotics is needed. Numerous environmental factors which affect the response to antibiotics cannot be adequately simulated in a laboratory situation. It is possible only through field evaluation to accurately assess the economic impact from use or restriction of use of antibiotics on animal production.

Considerable research has been devoted to the possible detrimental effects of drug use in animals on human health. There has been, however, little attention to the possible beneficial effects of antibiotic usage in animals on human health. Reduction in infections, abscesses, etc., may be of benefit to man and should be investigated.

Finally, research should be continued on methods of improving performance of animals without the use of drugs. Genetic resistance to disease, immunization to disease organisms and improved environment are all possible means of circumventing the need for antimicrobial drugs in animal production systems.

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